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# The American Journal of Syphilis

A QUARTERLY JOURNAL DEVOTED TO THE  
STUDY AND PREVENTION OF SYPHILIS

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## Original Articles

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### THE CHEMOTHERAPY OF MERCURIAL COMPOUNDS\*

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(Received for publication, December 19, 1916)

THE new science of chemotherapy has had its origin and its greatest impetus in the epoch-making researches of the distinguished and late lamented Paul Ehrlich. To the genius of this versatile chemist and biologist the world owes not only its conception of the principles of biochemical affinities, but also the practical fruition of these in the form of the most remarkable synthetic chemical compound known to man.

Ehrlich's interest in this subject dates back to his student days when he was attracted by an article by Heubel on lead poisoning; the anchoring of lead by the cells of the liver was doubtless the

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\*From the Dermatological Research Laboratories of the Philadelphia Polyclinic. Read at a meeting of the College of Physicians, Philadelphia, January 3, 1917.

initial observation that suggested the thought of selective affinities between protoplasm and chemical substances. Ehrlich's attention was then devoted to the influence of dyes such as fuchsin and methylene blue upon various tissues. His researches in dyestuffs led to his remarkable work on the differential staining of the blood cells, the demonstration of acid-fast fixation of tubercle bacilli, the diazo reaction of the urine, the methylene blue reaction on living nerve substance, etc. Later came the enunciation of his stimulating "side chain theory." His systematic investigations in chemotherapy began with the elaboration of a polyazo-dyestuff, which was capable of destroying trypanosomes, and which was consequently named "trypan-red." Compounds of phosphorous, antimony and arsenic were then studied in their various organic combinations. The demonstration that atoxyl, a combination of aniline oil and arsenic acid was capable of killing certain trypanosomes, was the awakening impulse that culminated, after painstaking and brilliant experimentation, in the elaboration of dioxydiamido-arsenobenzol dichlorhydrate, generally known as salvarsan.

Since the publication of Ehrlich's researches, investigators in different countries have turned their attention to mercury, a drug which has for 400 years been employed in the treatment of syphilis. Efforts have been made to create new mercurial compounds designed to exert a greater selective influence upon parasites, in particular, the spirochete of syphilis.

#### PREVIOUS RESEARCHES

*Literature.*—The development of organic mercury compounds was much stimulated by the fundamental researches of Dimroth,<sup>1</sup> who definitely proved that in the so-called organic mercury salts—for instance mercury salicylate—the metal was attached to one of the carbon atoms of the benzene ring, and not the carboxyl group. Dimroth prepared a number of new organic compounds with one valence of the metal taken up by an organic and the other by an inorganic group—hydroxyl, halogen or acetic acid radical. L. Pesci<sup>2</sup> succeeded in 1901 in preparing mercury dibenzoic acid, an organic compound with both mercury valences held by carbon atoms. E. Fischer and Mering<sup>3</sup> prepared in 1907 an analogous compound, *B*-mercury di-propionic acid, and found that it was considerably less toxic than the

ordinary mercurial compounds. In 1911 Schrauth, Schoeller and Müller<sup>4</sup> determined the same low toxicity for Pesci's mercury-dibenzoic acid. They believed that the mercury was so firmly bound to the carbon atoms as to be practically deprived of its metallic properties. Indeed, after injections of the compound intramuscularly into animals, they found almost the entire quantity eliminated in the urine unchanged. The last named investigators,<sup>5</sup> during their researches extending over a period of years, prepared a number of new organic mercury compounds, and studied them as to the degree of toxicity manifested in animals, and as to their antiseptic effect on parasites in the test tube. They claim to have established that the firmer mercury is bound to the organic radical, the less toxic does it become for the animal. Mercurials were divided by them into four classes: (a) inorganic, (b) pseudocomplex, (c) half complex, and (d) full complex compounds. In inorganic compounds mercury is precipitated by sodium hydroxide and certain other reagents; it on the other hand, precipitates protein from solutions.

In pseudocomplex compounds mercury is ionized to a lesser degree. Dilute sodium hydroxide solution does not precipitate it; ammonium and hydrogen sulphide do. In half complex compounds, mercury is more firmly attached to carbon and is not precipitated by any of the three reagents referred to in cold, but only on boiling. The full complex compounds have each valence of mercury bound to an organic radical so firmly that even boiling with strong reagents is without effect.

Schrauth and Schoeller<sup>6</sup> from their studies of large numbers of mercury compounds, are inclined to think that the therapeutically active substances are to be found in the class of half complex substances, because in full complex compounds, the mercury is so firmly bound that it loses its chemical and biological characteristics; for instance, the toxicity of such products is low, and the antiseptic effect is insignificant. In the pseudocomplex and in the inorganic form, mercury is so readily split off as to be highly toxic.

The same authors claim that some of the new mercury compounds which they have prepared are superior to known mercurials; one of these has appeared on the market under the trade name of "asurol." This is a double salt of sodium oxymercury-salicylate and sodium oxyisobutyrate containing about 40 per cent of mercury. W. Kolle

and Rothermundt<sup>7</sup> found it more toxic than mercury-salicylic acid (commonly called mercury salicylate) and of doubtful therapeutic value.

F. Blumenthal<sup>8</sup> and his coworkers have devoted considerable time and labor to an investigation of the toxicity and fate of mercury in the animal body. They believe that the therapeutic effect of mercury compounds bears a relationship to the extent to which mercury has an affinity for the cells of the liver, and as a result is deposited in this organ. Kolle and Rothermundt did not find this to be true in their experiments.

Blumenthal<sup>9</sup> studied the full complex mercury compounds prepared by Dr. Lüdecke of Charlottenburg, and found that the diamino-mercuri-diphenyl-carboxylic acid, and analogous dinitro and dihydroxy compounds are of lower toxicity than ordinary preparations of mercury. However, the antiseptic properties of these compounds in the test tube, were *nil*, and in human syphilis, as far as could be determined by the published literature, they were of little value. The sodium salt of acetylaminomercuribenzoic acid (marketed under the trade name of Toxynon) was prepared by Lüdecke and studied by Blumenthal; it is apparently a half complex compound and exhibited interesting biological properties in the earlier observations. It was later admitted by Blumenthal that it did not fulfill the expectations anticipated when the drug was employed in human syphilis.

Schilling, Von Krogh, Schrauth and Schoeller<sup>10</sup> carefully investigated the action of organic mercury compounds in experimental spirochetæ infections. Chicken spirillosis was found to be too feeble an infection to furnish conclusive data as to the curative influence of mercurial compounds, inasmuch as untreated animals frequently recovered from the experimentally induced disease.

Mercurial compounds were then tried out in mice infected with the spirochete of Obermeyer, the cause of relapsing or recurrent fever. A number of known compounds of mercury and new compounds prepared by the authors were tested and found to be of little value in combating this disease. Five new preparations, the chemical constitution of which was not disclosed, were regarded by the authors as superior to the others. Nothing appears, however, to have been further published concerning the therapeutic value of these preparations. The authors arrived at the conclusion that the



spirochete of relapsing fever in mice is not favorably influenced by mercurials, as both the infection and the medicament are too injurious to the intestines. The possibility of mercury having a stimulating effect upon the production of antibodies in the infected animal is a thought expressed by the authors, who hold that the same cannot be claimed for salvarsan, which has such a destructive effect upon the parasites that their antigenic properties are lost.

Kolle and Rothermundt<sup>11</sup> regarded chicken spirillosis as a favorable experimental infection to work with. Known mercurials which possess value in the treatment of syphilis, exhibit a favorable influence in chicken spirillosis. This fact makes the infection with the spirocheta gallinarum a good test for the determination of the value of new mercurial compounds. Experiments with "Asurol," dinitro mercuri-diphenyl-carboxylic acid and other new synthetic mercury compounds, demonstrated that they were not superior to any of the known preparations. The working hypothesis advanced by Blumenthal, that therapeutically active mercurial compounds must possess an affinity for liver cells, and the opinion of Schrauth and Schoeller concerning the necessity of mercury being firmly attached to the organic molecule in half complex form, were not concurred in by the authors; they invoked data based upon actual experimentation in support of their adverse views. They held that the therapeutic value of a mercurial preparation bore no relationship to the firmness of mercury in the molecule nor to the fact that the compound was a precipitant for protein, nor to the solubility or insolubility of the compound. The establishing of the therapeutic index was regarded by them as most important; i. e., the relationship of the *dosis lethalis* to the *dosis therapeutica*, as proposed by Ehrlich.

Kolle highly recommended a new compound prepared in his laboratories, which belonged apparently to the pseudocomplex class, and which was insoluble. This compound was placed upon the market under the trade name of "Argulan;" its chemical constitution shows it to be a sulfamino-antipyrene mercury compound. It is claimed by the authors that this preparation is as efficacious in the treatment of relapsing fever infection in mice as is salvarsan.

The therapeutic index in chicken spirillosis infection was found to be as high as 1/100; i.e., the relation of the curative dose to the toxic dose was 1 to 100. Argulan is claimed to be less organotropic than other mercurial compounds. It is administered to man by

intramuscular injection in oil, and exhibits favorable effects in the treatment of syphilis.

Hahn and Kostenbader<sup>12</sup> studied the pharmacological, physiological and therapeutic properties of a number of dyestuffs combined with mercury. Three classes of new compounds\* were investigated; mercury-phthaleins, mercury-anthrachinons and mercury-azodyes. The toxic dose was tested on mice and chickens. The therapeutic dose was tested out on chicken spirillosis. The authors claim to have obtained very favorable results in combating the infection with mercury dyestuffs, the therapeutic index being with many of the compounds close to 1/100. No relationship was found whatsoever between the toxicity and therapeutic effect on the one hand, and chemical and physical properties such as mercury content, solubility and ionization, on the other. The toxicity and curative effect apparently are to be explained by differences in the finer structure of the molecule. No "leads" could be found by the authors and therefore purely empirical investigation of whole groups of mercury compounds was proposed as the best possible way of securing an efficient therapeutic agent.

#### CHEMOTHERAPEUTIC STUDIES OF NEW MERCURIAL COMPOUNDS

In the following pages a study of the biological properties of a number of mercury compounds is presented. Some of these compounds were already known chemically, although we were not cognizant of this fact when they were prepared by us in our laboratories. Certain other of the mercury compounds referred to are, to the best of our knowledge, new, and prepared for the first time by us. These new preparations belong for the most part, to the group of half complex substances, the type which previous investigators believed to be the most fruitful source of therapeutically active compounds. In investigative work in this field, there are but few definitely established principles so that the researches must be in the beginning largely empiric. It is obvious, however, that without some systematic scheme in mind one might labor for years without practical results. To combine mercury in a haphazard manner with every chemical substance that suggested itself to one's mental vision, might by some fortuitous circumstance, eventuate in the production of a useful

\*These compounds were prepared by Saccharin Fabrik, actien gesell. Vorm, Fahlberg, List & Co., Magdeburg, Germany.

compound, but no scientific program could be mapped out along such lines. We endeavored to combine mercury with representatives of different groups of organic substances in order to find a "lead." Whenever one type of compound proved interesting, by reason of low toxicity combined with high parasiticide effect *in vitro* or *in vivo*, derivatives and substitution products of such substances were made and tested out. This work has been continued for about two years, and only recently have we been able to produce compounds of high promise. These are under study at the present time and consequently but brief mention of them will be made in this communication.

The following are some of the principal groups with which we have combined mercury; the resultant compounds were tested out on animals for toxicity and therapeutic effect, and their parasiticide properties studied in the test tube.

- a. Naphthol and Naphthylamine.
- b. Benzidine.
- c. Phenol.
- d. Dihydroxybenzene.
- e. Aminophenyl-arsenic acid.

The chemical properties and constitution of these compounds will be described and published elsewhere, inasmuch as their inclusion in this paper would expand it to undue proportions.

#### PLAN OF PROCEDURE

Our plan of procedure was first to study the toxicity of new compounds by injection of the substance into rabbits and into rats. Soluble compounds were administered intravenously to rabbits and the immediate dosis lethalis determined. The dosis tolerata was ascertained by graded amounts given intravenously to white rats. Insoluble products, of course, had to be studied by intramuscular injection. The previous investigations carried out by us<sup>13</sup> on the toxicity of the various mercurial compounds in use, was an excellent guide in establishing comparative values.

The conclusions reached in the article referred to are here briefly set forth:

1. Rats exhibit such variation in resisting power to mercurial compounds, that too much weight should not be attached to minor differences in toxicity in experimental findings.

2. While the maximum tolerated dose of the various compounds may be widely divergent, when the doses are calculated in terms of pure mercury, they fall within relatively narrow limits.

3. In general terms, it may be stated that the toxicity of the various mercurial compounds is directly proportionate to the amount of pure mercury contained.

4. The inorganic salts, as represented by the bichloride of mercury, are no more toxic than the numerous organic combinations that are commonly employed.

5. The differences in the molecular structure of the mercury compounds tested by us were found to be of relatively little importance as affecting their toxicity.

6. The bichloride of mercury was fatal, on the average, in intravenous doses above 2 milligrams per kilo of body weight; administered intramuscularly it was fatal on the average, above 6 mg. per kilo of body weight.

7. The average relationship as to the toxicity between the intravenous and intramuscular administration of mercury, in general, was about 4 to 1.

8. The insoluble preparations such as gray oil, calomel and the salicylate of mercury are absorbed in rabbits at the rate of a little over 1 per cent of the injected amount per day.

9. Even at the end of 6 or 7 weeks, almost 50 per cent of the mercury of insoluble preparations may be absorbed at the site of the injection in rabbits.

10. The injection of the usual doses of insoluble mercurial compounds at weekly intervals in the human subject, must invariably lead to accumulation of the drug in the tissues.

11. Insoluble mercurial injections should be given only by the skilled physician after careful consideration of the dose and of the intervals of administration.

12. Mercury has a great affinity for the cells of the kidney, and this organ is one of the earliest involved in mercurial intoxication. Hence during the intensive treatment with mercury, the necessity of careful examination of the urine from time to time should be emphasized.

13. The nephritis produced by mercury is primarily tubular in variety; capsular glomerulonephritis of the exudative (hemorrhagic) variety is frequent and practically always accompanies severe tubu-

lar nephritis. Calcification of the degenerated tubular cells has been found in animals within forty-eight hours after the administration of mercury and always occurs in severe mercury nephritis, irrespective of the salt administered or the route of injection.

It is readily comprehended that a medicament of value must not only be therapeutically active, but its toxicity must be such as to permit its use without serious damage to organs. Drugs may be of low toxicity and of low therapeutic effect; they may possess high curative properties but may be extremely poisonous. The ideal medicament is one which has a maximum therapeutic influence and a minimum toxic effect. In searching for the chemical substances possessing the power to destroy vegetable or animal parasites, it is essential that the biologic laboratory should be in close and constant co-operation with the chemical laboratory.

We have found the most satisfactory scheme for the investigation of the parasiticide properties of chemical compounds to be as follows:

1. The determination of the effect of the compounds upon bacteria in the test tube (a) by the germicidal test (Rideal-Walker), (b) by our so-called "antiseptic" test.
2. The determination of the effect of compounds upon trypanosomes and spirochetes in the test tube.
3. The determination of the effect of compounds on parasites in the test tube for definite periods, followed by the investigation of the infective power of the treated parasites by subsequent injection into animals. This is our so-called *test in vitro-vivo*.
4. The determination of the parasiticide and curative properties of compounds by injection into experimentally infected animals.

#### EXPERIMENTS IN VITRO

One may secure valuable information concerning the effect of medicaments upon bacterial life by studies of the action of the chemical substances under consideration, in the test tube. These tests can be carried out with reasonable rapidity, and fortunately yield quite constant results. Within a few days one can determine whether a given compound is capable of killing the staphylococcus, the bacillus typhosus, the pneumococcus or any other bacterium in the test tube, and the quantity of the compound and the time necessary to produce such effect. In this manner the bactericidal value of compounds for special organisms may be determined and compared.

This furnishes a valuable "lead," for the general proposition may be enunciated that substances which have a destructive effect upon bacteria in the test tube are *more apt* to have a germicidal influence in the living body than those which do not. This method permits one to eliminate from further consideration the inert compounds, and to continue the study of those which appear most promising. The above proposition must not be construed as an intimation that germicidal substances *in vitro* are prone to prove germicidal *in vivo*, for numerous complicated factors are here involved. The investigator in chemotherapy must be prepared to suffer many bitter disappointments with compounds which are most promising in the test tube and inert or relatively inert in the experimental animal.

#### GERMICIDAL OR RIDEAL-WALKER TEST

The technic of the germicidal test which we have employed is here briefly set forth:

These tests were conducted after the standard method employing varying dilutions of the chemical and a twenty-four-hour broth culture of *B. typhosus*.

Dilutions of the chemical under study were prepared in distilled water and placed in amounts of 5 c.c. in sterile test tubes in a water bath at 20° c. held in a special rack designed for these tests. Each five dilutions were then seeded with 0.1 c.c. of a twenty-four hour broth culture of *B. typhosus* and subcultures made at intervals of 2½ minutes up to 15 minutes, with a 4 mm. platinum loop and into tubes containing 10 c.c. of standard broth.

The results were recorded after forty-eight hours incubation at 37° C; with practice the method was found to yield uniform results. The results summarized in Table I were secured after several experiments with each compound to insure accuracy and constancy of result.

With each experiment phenol was employed in five different dilutions and the results of the tests with the mercurial compounds expressed in comparison with the germicidal activity of phenol (called the "phenol coefficient"). This comparison may be made with the 2½ or 15 minute periods of exposure as summarized in Table I, or, by averaging the results of the 2½ and 15 minute exposures, as is the practice in the standard test for determining and expressing the phenol coefficient.

TABLE I  
PHENOL COEFFICIENTS OF MERCURIAL COMPOUNDS FOR  $\beta$ -TYPHOSUS IN  
RIDEAL-WALKER METHOD

No.	Chemical Compound	Exposure in Minutes	
		2½	15
	Mercuric chloride.....	300	300
42	New mercuric compound, No. 42.....	5000	10,000
99	New mercuric compound, No. 99.....	10,000	10,000
100	Mercury-nitrosalicylic acid.....	100	100
105	New mercuric compound, No. 105.....	10,000	10,000

In Table I is observed the germicidal action on the typhoid bacillus of mercuric chloride (bichloride of mercury), and of several new mercury compounds prepared in our laboratory. It will be seen from an inspection of the figures, that the new compounds are incomparably superior to phenol and possess, moreover, a striking superiority over bichloride of mercury, which hitherto, in our experience had been the best mercurial germicide in the test tube. One of the new compounds, No. 99, is shown by this experiment (and this was repeated on several occasions) to be 300 times more germicidal than bichloride of mercury. This is shown in Table I.

It will be seen from this table that bichloride of mercury has 300 times the germicidal value of phenol, and that two of the new mercuric compounds have 10,000 times the germicidal value of phenol.

In the subjoined table (Table II) are represented the antiseptic values of a number of mercuric compounds, both known and new. Without going into detail it will be seen that the values vary very greatly and that the antiseptic effect of the various compounds is not related to the content of pure mercury in the substance, but rather to the chemical constitution of the molecule. It is of particular interest to note that the new mercurial compound No. 99 has exhibited the maximum effect by the antiseptic test, just as it has equalled the highest coefficient by the germicidal method. Many of the new mercuric compounds made by us exceed bichloride of mercury in antiseptic power. No. 99 kills the staphylococcus aureus in a dilution of 1 to 5 million, whereas bichloride of mercury kills only in a dilution of 1 to 100,000.

As a matter of general interest in connection with this test, the antiseptic value of salvarsan and arsenobenzol (Dermatological Research Laboratories) is likewise given. It will be seen that they

both kill the staphylococcus in dilution of 1 to 2000 and thus show a marked inferiority as compared with bichloride of mercury.

It is proper to add that these tests were made three times in order to eliminate, as far as possible, errors in the result.

TABLE II  
BACTERICIDAL ACTIVITY OF MERCURIAL COMPOUNDS IN THE "ANTISEPTIC" TEST

Laboratory Number of Compound	Chemical Compound	Bactericidal Dilution	
		Staph. aureus	β-typhosus
42*	New mercury compound No. 42.....	1:1,000,000	1:500,000
41*	Hexamethylenetetramine mercuric acetate	1:330,000	Not performed
104*	Mercury-amino-salicylic acid.....	1:250,000	"
100*	Mercury-nitrosalicylic acid.....	1:500,000	"
95*	Mercury-nitrophenylarsinic acid.....	1:110,000	"
96*	Mercury-amino-oxyphenylarsinic acid....	less than 1:100,000	"
97*	Dimercurey-diacetyldiamino-oxyphenylarsinic acid.....	1:200,000	"
98*	New mercury compound No. 98.....	1:330,000	"
99*	New mercury compound No. 99.....	1:5,000,000	"
9	Resorcin-mercuric acetate.....	1:500,000	"
101	Thymol mercuric acetate.....	1:330,000	"
2	β-naphthol-mercuric acetate.....	less than 1:100,000	less than 1:100,000
39*	Sulpho-β-naphthylamine-mercuric acetate..	less than 1:100,000	less than 1:100,000
41	Hexamethylenetetramine-mercuric acetate	less than 1:100,000	less than 1:100,000
	Mercuric chloride (bichloride) of Hg.....	1:160,000	1:200,000
	Calomel.....	1:140,000	1:160,000
	Mercury-benzoic acid.....	1:160,000	1:160,000
	Mercury-cacodylic acid.....	1:100,000	1:100,000
	Mercury-salicylic acid.....	1:160,000	1:200,000
	Arsenobenzol.....	1:2000	1:2500
	Salvarsan.....	1:2000	1:2500

\*New mercury compounds prepared in our laboratories. Performed in triplicate.

*Technic.*—In conducting this test small numbers of the test micro-organism were exposed to high dilutions of chemicals over a period of several days.

The stock solutions of chemicals were prepared by dissolving 0.010 mg. in 100 c.c. of sterile distilled water. Amounts varying from 0.1 c.c. to 1.0 c.c. were then placed in a series of ten sterile test tubes of appropriate size followed by the addition of sufficient plain neutral and sterile broth to make the total volume in each tube 10 cubic



centimeters. Each tube and several controls were then seeded with 0.05 c.c. of a twenty-four hour broth culture of staphylococcus aureus. All cultures were incubated at 37° C. for about five days when the results were recorded. Sterility was indicated by perfectly clear tubes and in many instances these results were checked by further subcultures to determine whether or not actual death of all cocci had occurred rather than an inhibition. Readings made at the end of twenty-four hours were always higher than those made after the expiration of five days; the former may be designated the anti-septic or inhibiting dose and the latter, the germicidal or killing dose. Further details regarding this method which we have found very simple and remarkably uniform in its results, will be found in our former publications.<sup>14, 15</sup>

BACTERICIDAL ACTIVITY IN A MENSTRUUM OF SERUM  
(PIPETTE METHOD)

Of considerable importance in relation to the bactericidal activity of compounds *in vitro* and to the problems of the chemotherapy of bacterial infections, is the question of the maintenance of the bactericidal activity of a given substance in a menstruum of serum. With many substances as bichloride of mercury and phenol, the bactericidal values are considerably lower in serum than in normal salt solution or nutrient broth. In general terms the compound which maintains a high degree of bactericidal activity *in vitro* in a menstruum of serum or ascites fluid is to be regarded as superior inasmuch as the conditions of such an experiment approach more closely those existing in the living body. We have tested a number of mercurial compounds both known and by the new pipette method, the technic and results appearing in the following table (Table III.)

*Technic.*—In this method varying dilutions of the chemical under study were prepared in sterile ascites fluid in a series of small sterile tubules in amount of 1 cubic centimeter. To each tubule was then added 0.2 c.c. of twenty-four hour broth culture of *B. typhosus* followed by gentle mixing. At intervals of 5, 15, 20 and 30 minutes a small amount of each dilution was cultivated in broth contained in the bulbous portions of capillary pipettes. We have also conducted this test by using one capillary pipette marked to carry a definite volume, and transferring an equal amount of each dilution to tubes containing 10 c.c. of broth. The pipette is sterilized between each

transfer by several washings with boiling salt solution placed alongside of the worker. In this manner the amount of drug actually transferred is quite small and undergoes very high dilution in the broth so that any resultant germicidal action takes place in the menstruum of ascites fluid or blood serum. The results of tests shown in Table III were conducted in this manner. All tubes or pipettes were incubated for three days and the results read and checked by subcultures.

Further details of this method, which we have found best suited for germicidal tests in a menstruum of serum, will be found in one of our former communications.<sup>16</sup>

TABLE III  
BACTERICIDAL ACTIVITY OF PHENOL AND MERCURIAL COMPOUNDS UPON  
STAPHYLOCOCCUS AUREUS IN A MENSTRUUM OF ASCITES FLUID (PIPETTE METHOD)

No.	Chemical Compound	Bactericidal		Bichloride Coefficient (5 minutes)
		5 min.	30 min.	
	Mercuric Chloride.....	1:8000	1:32,000	
	Phenol.....	less than 1:40	less than 1:40	
	New mercury compound No. 42....	1:400,000	1:800,000	50
	New mercury compound No. 99....	more than 1:1,600,000	more than 1:1,160,000	200
	Mercury nitro-salicylic acid.....	1:50,000	1:50,000	6
	New mercury compound No. 105....	1:400,000	1:1,160,000	50

As shown in Table III, two of our new mercurial compounds (No. 42 and No. 105) exhibited a bactericidal activity in ascites fluid 50 times higher than that exerted by bichloride of mercury, while our new compound No. 99, was found 200 times more powerful.

#### SPIROCHETICIDAL ACTIVITY OF SALVARSAN, ARSENOBENZOL (DERMATOLOGICAL RESEARCH LABORATORIES) AND MERCURIAL COMPOUNDS IN VITRO

The superiority of salvarsan and arsenobenzol as spirocheticidal compounds is demonstrable by tests *in vitro*. The results of a few such tests with these and mercurial compounds are shown in Table IV; we have not been able to repeat these experiments frequently enough to present the results as absolute, and further studies may necessitate a revision of the values shown, but the results are sufficiently conclusive to demonstrate a spirocheticidal activity of salvarsan and mercurial compounds *in vitro* for the spirochete of

syphilis; the former are more active in this respect. All of the experiments shown in Table IV were conducted with the same strain of pallida and within a few days of each other, so that the variations in results may be attributable to the different products or slight errors in technic.

The technic employed was as follows:

*Technic.*—These tests were conducted with a pure culture of spirocheta pallida received some months previously from Dr. Hans Zins-

TABLE IV  
THE SPIROCHETICIDAL ACTIVITY OF SALVARSAN, ARSENOBENZOL (DERMATOLOGICAL RESEARCH LABORATORIES) AND MERCURIAL COMPOUNDS FOR SPIROCHETA PALLIDA *in vitro*\*

Final Dilutions	Compounds					
	Salvarsan No. A	Salvarsan No. B	Arseno-benzol No. A	Arseno-benzol No. B	Bichloride of Mercury	New Mercurial Compound No. 2
1:20	— **	—	—	—	—	—
1:40	—	—	—	—	—	—
1:80	—	—	—	—	—	—
1:160	—	—	—	—	—	—
1:320	—	—	—	—	+	—
1:1000	—	—	—	—	+	—
1:2000	—	—	—	—	+	+
1:4000	+	—	—	+	+	+
1:8000	+	—	—	+	+	+
1:16000	+	—	—	+	+	+
1:32000	+	—	—	+	+	+
1:64000	+	—	—	+	+	+
1:128,000	+	+	—	+	+	+
1:256,000	+	+	+	+	+	+
1:512,000	+	+	+	+	+	+

\* all controls yielded good growths of Sp. pallida.

\*\* sterile.

\*\*\* growth of S. pallida.

ser (strain A). The spirochetes of this culture grew well in appropriate solid and fluid culture media.

A stock solution of the compound under study was prepared in sterile distilled water and varying dilutions in amounts of 1 c.c. prepared in a series of sterile test tubes with sterile broth. To each tube of this series and several controls, was added 1 c.c. of a fluid ascites broth culture of pallidum, which had been gently shaken with sterile beads to break up clumps and which showed in each micro-

scopic field about forty or more active spirochetes by dark-field illumination. After gentle mixing, the tubes were incubated for two hours at 37° C. when a piece of sterile rabbit kidney and eight cubic centimeters of ascites agar were added to each tube. This made the dilution ten times greater, but those given in the adjoining table were the dilutions of drug to which the spirochetes had been exposed prior to the addition of the culture medium. No doubt the influence of the compounds was continued after dilution with ascites agar. Each tube was covered with sterile paraffin oil and incubated at 37° C. for three to five weeks. At the end of this time each tube was examined by dark-field illumination for active spirochetes by removing portions of the medium at different levels with sterile capillary pipettes. All of the controls showed numerous active spirochetes; it was found impossible to express an opinion as to diminution in numbers of spirochetes as the number varied in different parts of the culture medium. The results, therefore, are expressed as sterile or showing a growth, and are given in Table IV.

#### TIHERAPEUTIC EXPERIMENTS IN ANIMALS

*Method of Study.*—In our investigations of the action of mercury and arsenicals in animal infections, the following four parasites have been employed: the spirocheta recurrentis (the parasite of relapsing fever), the Trypanosoma brucei (the parasite of Nagana disease of horses), the Trypanosoma lewisi (a saprophytic parasite in rats), and the Trypanosoma equiperdum (the parasite of “la dourine” or horse syphilis).

Inasmuch as the influence of the drug administered on the duration of life of the infected animals is one of the important criteria of its efficiency, we found the Trypanosoma lewisi unsatisfactory because it does not as a rule kill the animal. The spirochete of relapsing fever leads to confusing results because of the frequent remissions and the disappearance of the parasite from the peripheral blood. The Trypanosoma brucei kills rats within a few days, a period too short to study the effects of the weaker agents. The Trypanosoma equiperdum was found admirably adapted to the purposes of our studies, and was the parasite generally employed by us. It kills the rats within four to seven days after infection, depending upon the infecting dose and upon the virulence of the strain.

Our investigations latterly have been carried out routinely against the *Trypanosoma equiperdum* inoculated into white rats.

*Technic.*—Our therapeutic test is conducted by injecting rats intravenously with a dose of the drug corresponding to body weight, twenty-four hours after the animals have been infected by injecting the test microparasite intraperitoneally. In this manner the infection has a start of twenty-four hours and is well established before the drugs are administered. All intravenous injections are given into the external jugular vein which permits the injection of accurate doses. Each animal is weighed and individual doses are prepared according to 100 grams of body weight. In each experiment four control animals are included; these are infected but receive no drug.

Of considerable importance in these tests is the number of microparasites used in infecting the experimental animals. Infection with very large numbers of pathologic trypanosomes yields an overwhelming infection which effectually obscures any therapeutic result.

In our experiments the animals are infected with approximately known numbers of trypanosomes after the method of Kolmer and in such a manner as to result in a regular and uniform infection without being overwhelming. The importance of this numerical relationship of infection to experimental trypanosomiasis has been studied experimentally and our results reported elsewhere.

The blood of each animal is examined daily and the number of parasites in the peripheral blood recorded after the following scheme:

- few = one to two per field or every other field.
- + = about 5 to 10 in a field.
- ++ = about 10 to 20 in a field.
- +++ = large numbers that may be roughly, but not accurately counted.
- ++++ = very large numbers; cannot be counted.

The effects of a chemical are studied by its power to permanently sterilize or its power of inhibiting the proliferation of the microparasite and prolonging the life of the animal. These effects are readily determined by comparison with the controls.

In Table V, VI and VII are noted the effects in experimental trypanosomiasis of a number of commonly employed mercurial compounds:

TABLE V  
INFLUENCE OF MERCURIAL COMPOUNDS ADMINISTERED INTRAVENOUSLY  
TWENTY-FOUR HOURS AFTER INFECTION WITH *T. EQUIPERDUM*\*

Subst.	No.	Wt. in gms.	Dose per 100 grams	Daily Examinations						
				1	2	3	4	5	6	7
Mercuric Chloride	1	85	.0003	—	few	D				
	2	89	.0002	—	few	++	++++	D		
	3	100	.0001	—	few	++	++++	D		
	4	111	.0001	—	few	+	++	++++	D	
Mercury-Benzoic Acid	5	62	.0003	—	++	D				
	6	52	.0003	—	+	++++	++++	D		
	7	60	.0002	—	+	++++	++++	++++	++++	D
	8	42	.0001	—	++	++++	++++	++++	D	
Mercury-Succinimide	9	49	.0003	—	+	++++	++++	D		
	10	63	.0003	—	+	+++	+++	++++	D	
	11	66	.0002	—	+	++	++++	++++	++++	D
	12	55	.0001	—	+	+++	++++	D		
Mercury-Cacodylic Acid	13	61	.0003	—	+	+++	++++	++++	D	
	14	75	.0003	—	+	++	+++	D		
	15	54	.0002	—	+	++++	++++	++++	D	
	16	48	.0001	—	+	++++	++++	D		
	17	48	control	—	+	++	++++	++++	++++	D
	18	66	control	—	+	+++	++++	D		
	19	54	control	—	+	++	++++	++++	++++	D
	20	50	control	—	+	++	++++	++++	D	

\* Rats infected with 120,000 trypanosomes by intraperitoneal injection.  
D Signifies death of animal.

It will be seen that the injections of bichloride of mercury and the other mercurials in doses as large as can be borne by the animal, have no material influence in lessening the number of trypanosomes in the blood nor of prolonging the life of the animal. This can be readily determined by comparison with the control rats, which of course did not receive any medication.

Table VI exhibits the results of the administration of a number of mercurials made in our laboratory. As will be observed, none of these have been able to inhibit the multiplication of the parasite, nor of prolonging life.

In Table VII the effect of several new mercurial compounds which gave brilliant results as bactericides, is shown. In two instances an inhibitory influence is noted at the end of 48 hours, but all of the animals died shortly after the death of the controls.

TABLE VI  
INFLUENCE OF MERCURIALS ADMINISTERED INTRAVENOUSLY TWENTY-FOUR  
HOURS AFTER INFECTION WITH *T. EQUIPERDUM*\*

Subst.	No.	Wt. in gms.	Dose per 100 grams	Daily Examinations				
				1	2	3	4	5
No. 2 $\beta$ -naphthol- Mercuric Acetate	1	60	.0003	—	+	++	++++	D
	2	72	.0002	—	+	++	D	
	3	72	.0001	—	+	++++	++++	D
	4	73	.00005	—	+	++	++++	D
Hexamethy- lene-tetramine- mercuric- Acetate	5	62	.0003	—	+	D		
	6	67	.0002	—	+	D		
	7	79	.0001	—	+	++++	++++	D
	8	69	.00005	—	few	++	++++	D
Sulpho-- $\beta$ - naphthylamine mercuric Acetate	9	139	.0003	—	+	++	D	
	10	109	.0002	—	++	+++	D	
	11	97	.0001	—	+	++++	++++	D
	12	132	.00005	—	+	++++	D	
Mercury- aminophenyl- arsinic acid	13	151	.0005	—	few	+++	D	
	14	128	.0004	—	few	+	++	D
	15	100	.0003	—	—	+	++++	D
	16	96	.0002	—	+	++	++++	D
	17	83	control	—	+	++	++++	D
	18	67	control	—	+	+++	D	
	19	64	control	—	+	++	++++	D
	20	63	control	—	+	+++	++++	D

\*Rats infected with 90,000 to 124,000 trypanosomes by intraperitoneal injection.

Space will not permit a detailed tabular presentation of the various experiments with different microparasites. It will perhaps suffice to summarize these in the following tables, VIII and IX:

In the above table the summarized results of the maximum dose of various mercurial compounds is given. In a general way it is seen that the new compounds exhibit a slightly restraining influence upon the appearance of trypanosomes in the blood, whereas this result is not obtained by the bichloride of mercury, although this substance contains a much higher percentage of mercury (73%).

It must be remembered that in biological work of this character discrepancies will arise from time to time, owing to differences in the virulence of the infecting strain, the individual resistance of the rats and other complex factors. Mathematically precise results cannot be hoped for in investigations of this character. It is only by frequent repetition of experiments and careful comparison of the

TABLE VII  
INFLUENCE OF MERCURIAL COMPOUNDS ADMINISTERED INTRAVENOUSLY  
TWENTY-FOUR HOURS AFTER INFECTION WITH *T. EQUIPERDUM*\*

	No.	Wt. in gms.	Dose per 100 grams	Daily Examinations				
				1	2	3	4	5
New mercury compound No. 99	1	85	.0008	—	D			
	2	134	.0007	—	++	D		
	3	99	.0006	—	++	D		
	4	80	.0004	—	++	D		
Mercury- nitro-oxyphenyl- arsinic acid	5	82	.0012	—	—	few	+++	D
	6	94	.001	—	+	++++	D	
	7	78	.0008	—	++	D		
	8	64	.0006	—	++	++++	D	
Mercury- nitrosalicylic acid	9	109	.0008	—	++	++++	D	
	10	64	.0007	—	++	++++	++++	D
	11	55	.0006	—	++	++++	D	
	12	107	.0004	—	++	D		
New mercury compound No. 105	13	82	.0008	—	+	++++	++++	D
	14	109	.0007	—	—	+	++	D
	15	85	.0006	—	few	++	D	
	16	110	.0004	—	++	++++	D	
	17	80	control	—	++	D		
	18	79	control	—	++	++++	D	
	19	89	control	—	++	D		
	20	59	control	—	++	++++	D	

\*Rats infected intraperitoneally with 250,000 trypanosomes.

TABLE VIII  
INFLUENCE OF MERCURIAL COMPOUNDS ADMINISTERED INTRAVENOUSLY  
TWENTY-FOUR HOURS AFTER INFECTION WITH *S. OBERMAYERI*

Laboratory No. of Compound	Name of Compound	Maximum Dose per 100 gms.	Equivalent per 60 K. (125 lbs.)	Effect on Spiroch- etes
28*	$\beta$ -Naphthylamine-azo- $\beta$ -naphth- olmercuric acetate.....	.01	6.0	Inhibition for 6 days
24	Mercury-benzoic acid.....	.0004	0.24	None
30*	Sulpho- $\beta$ -naphtholmercuric ace- tate.....	.0008	0.48	None
2	$\beta$ -naphthol-mercuric acetate.....	.0006	0.36	Inhibition for 24 hrs.
27*	Amido-benzol-sulpho-azo- $\beta$ - naphthol-mercuric acetate.....	.001	0.6	None
	Mercury.....	.0003	0.18	None
	Mercury-Salicylic acid.....	.0004	0.24	None

\*New compounds made in our laboratories.

\*This compound is commonly but erroneously termed mercury salicylate.



TABLE IX  
INFLUENCE OF MERCURIAL COMPOUNDS ADMINISTERED INTRAVENOUSLY  
TWENTY-FOUR HOURS AFTER INFECTION WITH T. EQUIPERDUM

Laboratory No. of Compound	Name of Compound	Maximum Dose per 100 gms. body wt.	Equivalent per 60 K. (125 lbs.) body wt.	Effect on Trypanosomes
95*	Mercury-nitro-oxyphenylarsinic acid.....	.0012	0.72	None
71*	Mercury-amino phenylarsinic acid	.0005	0.3	None
6	$\beta$ -naphthol-mercuric oxide.....	.0003	0.18	Inhibition for 24 hrs.
2	$\beta$ -naphthol-mercuric acetate.....	.0006	0.36	None
27*	Amido-benzol-sulpho-azo- $\beta$ -naphthol-mercuric oxide.....	.001	0.6	None
3*	Mercury-o-sulphamid benzoic acid	.00058	0.348	None
41*	Hexamethylene-tetramine-mercuric acetate.....	.0004	0.24	None
39*	Sulpho- $\beta$ -naphthylamine mercuric acetate.....	.0003	0.18	Inhibition for 24 hrs.
42*	New Mercuric Compound No. 42	.0004	0.24	Inhibition for 24 hrs.
	Mercury Succinimide.....	.0004	0.24	None
	Mercury-cacodylic acid **.....	.0004	0.24	None
	Mercuric chloride.....	.0003	0.18	None
	Mercury-benzoic acid **.....	.0003	0.18	None or inhibition for 24 hrs.
	Mercury oxycyanide.....	.0002	0.12	None
	Mercury-salicylic acid **.....	.0004	0.24	None
	Mercury sozoiodolate.....	.0003	0.18	None

\*\*These compounds are commonly but erroneously termed mercury salicylate, mercury cacodylate, etc.

\*New compounds made in our laboratories.

conditions under which they are conducted, that the results can be scientifically reconciled.

The experiments above referred to constitute a most severe test of the action of a parasiticide agent, inasmuch as the infection is given 24 hours start before the medicament is injected into the blood stream. The following table (Table X) exhibits the results of an experiment in which the infection is given merely two hours' start, before the remedial drug is infused into the veins. The new mercurial compounds were chiefly tested by this method and varying degrees of inhibition are observed. In one instance the blood was kept free of parasites for four days.

TABLE X  
INFLUENCE OF MERCURIAL COMPOUNDS ADMINISTERED INTRAVENOUSLY  
TWO HOURS AFTER INFECTION WITH *T. EQUIPERDUM*

Laboratory No. of Compound	Chemical Compounds	Maximum Dose per 100 gms.	Equivalent per 60 K. (125 lbs.)	Effect on Trypan- osomes
99	New mercury compound No. 99..	.0008	0.48	Inhibition for 4 days
95	Mercury-nitro-oxyphenylarsinic acid.....	.0012	0.72	None
100	Mercury-nitrosalicylic acid.....	.0008	0.48	Inhibition for 24 hrs.
105	New mercury compound No. 105.	.0008	0.48	Inhibition for 24 hrs.
42	New mercury compound No. 42..	.0007	0.42	Inhibition for 24 hrs.

As indicating the great superiority of salvarsan and its congeners over mercury in experimental trypanosomiasis, the following table (Table XI) is presented. Here the picture is quite different from those shown above.

Numerous experiments carried out by us show that salvarsan in the dose of 15 mg. per kilo of body weight, is capable of sterilizing white rats infected with the *T. equiperdum*. Only with doses below this, do the parasites appear in the blood, and the time of their appearance is in inverse ratio to the size of the sub-curative dose administered. The chart also exhibits the therapeutic effect of the arsenobenzol prepared in our laboratories. Neosalvarsan is seen to be inferior in its effect to salvarsan. Salvarsan is likewise capable of sterilizing animals infected with the spirochete of relapsing fever, an organism more closely related to the organism of human syphilis.

#### THE TRYPANOCIDAL ACTIVITY OF VARIOUS COMPOUNDS IN THE COMBINED IN VITRO-VIVO TEST

During the course of chemotherapeutic studies, compounds possessing a well defined parasitotropic effect may be prepared, which prove so highly organotropic or toxic for the test animal, that the minute doses tolerated fail to exert an appreciable influence upon the parasites. The mercurials, which are known to exert a powerful bactericidal effect *in vitro* are substances of this class, being so highly toxic that doses greater than 0.0004 gm. per 100 grams of white rat are apt to prove fatal and yet too small to materially influence the course of experimental trypanosomiasis.

TABLE XI  
INFLUENCE OF SALVARSAN, ARSENOBENZOL (DERMATOLOGICAL RESEARCH LABORATORIES) AND NEOSALVARSAN ADMINISTERED  
INTRAVENOUSLY TWENTY-FOUR HOURS AFTER INFECTION WITH T. EQUIPERDUM\*

Subst.	No.	Wt. in Gms.	Dose per 100 grams of Body Weight	Results of Daily Examinations of Blood From Tail														
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Salvarsan B. F. U.	1	127	.004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	2	90	.003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	3	124	.002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	4	112	.001	-	-	-	-	-	-	few	+	++++	++++	D				
Arseno- benzol No. 54	5	97	.004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	6	85	.003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	7	89	.002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	8	103	.001	-	-	-	-	-	-	-	-	-	few	+	++	++++	D	
Neosalvarsan	9	112	.004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	10	82	.003	-	-	-	-	-	-	-	-	-	+	++	++++	++++	D	
	11	98	.002	-	-	-	-	-	-	-	few	+	++++	++++	D			
	12	75	.001	-	-	-	-	-	-	few	+	++++	D					
	13	90	control	few	++	++++	D											
	14	101	control	few	++	++++	D											
	15	75	control	few	++	++++	D											
	16	83	control	few	++	++++	++++	D										

\* Rats infected with 180,000 trypanosomes by intraperitoneal injection.

D Signifies death of animal.

In order, therefore, to avoid the mistake of discarding new compounds possessing a high degree of trypanocidal activity because they are highly toxic for experimental animals, a study of various methods of determining the trypanocidal activity of a drug independent to some extent of its toxicity for the body cells of the host, was undertaken with the result that we have succeeded in devising a valuable technic for these purposes. In the event of the preparation of a new compound which is highly toxic, but also possessing a high degree of parasitropism, our efforts are devoted toward lowering its toxicity to a sufficient extent to permit the administration of the drug to living animals.

We have studied various methods in detail, the results being given elsewhere;<sup>19</sup> according to these experiments our combined *in vitro-vivo* method yielded the most constant and reliable results.

*Technic.*—In this method equal parts of varying dilutions of the chemical under study are mixed with blood-trypanosome emulsion and kept at 37° to 40° C. for 15 minutes, when the whole or a part is injected intraperitoneally into white rats to determine the degree of trypanocidal activity. As a part of the drug is injected, the action of the drug is both *in vitro* and *in vivo* and due care must be exercised against the administration of lethal doses of the drug.

Each rat is then kept under observation for at least two weeks and the blood examined daily for trypanosomes. In this manner the degree of trypanocidal activity may be determined according to the time when trypanosomes appear and the duration of life as compared with the controls, or whether the animals remain sterile for an indefinite period of time.

The influence of various well known mercurial compounds and phenol upon *T. equiperdum* in this test, is shown in Table XII.

The results demonstrate that these mercurial compounds are capable of exercising an influence upon trypanosomes, which effect is not apparent in tests *in vivo* due probably to the high toxicity of these compounds and the necessity of administering relatively small doses (Table XIII).

The results of tests with certain new mercurial compounds are shown in Tables XIV, XV and XVI.

The remarkably high trypanocidal activity of arsenobenzol in this test, is shown in Tables XVII and XVIII.

TABLE XII  
EFFECT OF MERCURIAL COMPOUNDS AND PHENOL UPON T. EQUIPERDUM IN THE COMBINED TEST IN VITRO-VIVO

	No.	Wt. in Gms.	Dilutions	Amount in Grams	Results of Daily Examination of Tail Blood											
					1	2	3	4	5	6	7	8	9	10	11	12
Mercuric Chloride	1	105	1:2500	.0004	-	-	-	D								
	2	160	1:5000	.0002	-	-	-	-	D							
	3	102	1:10,000	.0001	-	-	-	-	few	++	+++	++++	D			
	4	128	1:20,000	.00005	-	-	-	-	-	-	-	-	few	few	+	+++
	5	100	1:40,000	.000025	-	-	-	-	-	few	+	++++	D			
Mercury Salicylic Acid	6	132	1:2500	.0004	-	-	-	D								
	7	102	1:5000	.0002	-	-	-	-	D							
	8	85	1:10,000	.0001	-	D										
	9	94	1:20,000	.00005	-	-	-	-	-	D						
	10	103	1:40,000	.000025	-	-	-	-	-	-	-	-	-	-	few	
Calomel	11	100	1:2500	.0004	-	few	few	D								
	12	82	1:5000	.0002	-	-	+++	D								
	13	85	1:10,000	.0001	few	+	+++	D								
	14	89	1:20,000	.00005	few	+	+++	D								
	15	76	1:40,000	.000025	few	+	+++	D								
Phenol	16	100	1:100	.01	-	-	-	-	D							
	17	87	1:200	.005	-	-	-	-	-	-	-	-	+	+++	++++	D
	18	77	1:400	.0025	-	-	-	-	D							
	19	87	1:800	.00125	-	-	few	++	++++	D						
	20	93	1:1600	.000625	few	+	+++	++++	++++	D						
Controls	21	76	0	0	few	+	++++	D								
	22	70	0	0	few	+	++++	D								
	23	58	0	0	few	+	++++	D								
	24	78	0	0	few	+	++++	D								

TABLE XIII  
COMPARISON OF THE TRYPANOCIDAL ACTIVITY OF BICHLORIDE OF MERCURY IN THE VIVO AND THE COMBINED VITRO-VIVO METHODS\*

Method	No.	Wt. in Gms.	Dose	Results of Examination of Blood From Tail														
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Routine In Vivo	1	49	.0003**	+	+++	++++	D											
	2	66	.0002	+	++	++++	++++	D										
	3	55	.0001	+	+	+++	++++	D										
	4	70	.00005	+	++	++++	D											
	5	80	control	+	+++	++++	D											
	6	65	control	+	+++	++++	D											
Combined Vitro-Vivo	7***	78	.0004*****	-	-	-	D	*****										
	8	70	.0002	-	-	-	-	-	few	+	+++	++++	++++	D				
	9	95	.0001	-	-	-	-	-	few	+	++	++++	D					
	10	95	.00005	-	-	-	-	few	+	+	++++	D						
	11	108	.000025	-	-	few	few	+	+	++	++++	D						
	12	90	control	-	-	few	+	++++	++++	++++	D							
	13	70	control	-	-	few	+	++++	++++	++++	D							
				-	-	few	+	++++	++++	++++	D							

\*Rats infected by intraperitoneal injection with 120,000 T. equiperdum twenty-four hours before the intravenous administration of bichloride of mercury.

\*\*Doses of bichloride of mercury per 100 grams of body weight.

\*\*\*Combined Vitro-Vivo Method conducted with 12,000,000 T. equiperdum.

\*\*\*\*Amount of bichloride of mercury to which the trypanosomes had been exposed for 15 minutes in vitro.

\*\*\*\*\*Probably death due to toxicity of mercury.











TABLE XVIII  
EFFECT OF ARSENOBENZOL UPON T. EQUIPERDUM IN THE COMBINED TEST IN VITRO-VIVO

No.	Wt. in Gms.	Dilutions	Amount in Grams	Results of Examination of Tail Blood in Days											
				1	2	3	4	5	6	7	8	9	10	11	12
1	90	1:1000	.001	-	-	-	-	-	-	-	-	-	-	-	-
2	83	1:2000	.0005	-	-	-	-	-	-	-	-	D	-	-	-
3	84	1:4000	.00025	-	-	-	-	-	-	-	-	-	-	-	-
4	72	1:8000	.000125	-	-	-	-	-	-	-	-	-	-	D	-
5	110	1:16,000	.0000625	-	-	-	-	-	-	-	-	-	-	-	-
6	80	control	0	few	few	few	+	++	++	D	-	-	-	-	-
7	91	control	0	-	-	-	few	+++	D	-	-	-	-	-	-
8	97	control	0	-	few	few	+	+	+	++	++	D	-	-	-
9	82	control	0	-	few	+	+++	+++	+++	D	-	-	-	-	-

In charts XV and XVI it is seen at a glance that the new mercuric compounds Nos. 99, 105 and 42, in which we are so much interested, are distinctly superior to bichloride of mercury in their trypanocidal effect by this method. There is much reason to believe that the effect exerted in this test is largely *in vitro*, but the determination of the results is obtained by an experiment *in vivo*.

TABLE XIX

INFLUENCE OF MERCURIAL COMPOUNDS ADMINISTERED INTRAVENOUSLY  
TWENTY-FOUR HOURS AFTER INFECTION WITH *T. BRUCEI*

Laboratory No. of Compound	Name of Compound	Maximum Dose per 100 gms.	Equiva- lent per 60 K. (125 lbs.)	Effect on Trypan- osomes
41	Hexamethylenetetramine-mercuric acetate.....	.0004	0.24	None
39	Sulpho- $\beta$ -naphthylamine-mercuric acetate.....	.0005	0.3	None
34	Disulpho- $\beta$ -naphtholmercuric oxide.....	.0005	0.3	None
42	New mercury compound.....	.0004	0.24	None
46	Pyridinemercuric acetate.....	.0003	0.18	None
35	Sulpho-benzidenemercuric acetate	.0004	0.24	None

TABLE XX

INFLUENCE OF MERCURIAL COMPOUNDS ADMINISTERED INTRAVENOUSLY  
TWENTY-FOUR HOURS AFTER INFECTION WITH *T. LEWISI*

Laboratory No. of Compound	Name of Compound	Maximum Dose per 100 gms.	Equiva- lent per 60 Kilos (125 lbs.)	Effect on Trypan- osomes
3	Mercury-o-sulphamid benzoic acid	.0006	.....	None
28	$\beta$ -Naphthylamin-azo- $\beta$ -naphtholmercuric acetate.....	.0006	.....	Inhibition for 6 days
2	$\beta$ -Naphtholmercuric acetate.....	.0006	.....	None
27	Amidobenzolsulpho-azo- $\beta$ -naphtholmercuric oxide.....	.0006	.....	None

*The Effect of Mercury Compounds on T. brucei and T. lewisi.*—In the preceding charts the experiments with various mercurial compounds have been detailed in their effect on the *T. equiperdum*. We have also carried out a series of tests with various compounds on the *T. brucei*, the organism which causes Nagana disease of horses. Below is presented a chart (Table XIX) showing the maximum dose of the different compounds employed. Inasmuch as the highest dose

used had no effect on the trypanosomes, it is unnecessary to give a detailed table of each experiment.

The *T. equiperdum* and the *T. brucei* are both microorganisms which kill infected animals within a short period of time. It was thought that we might possibly accomplish more with mercurials in the treatment of rats infected with the *T. lewisi* inasmuch as this organism is saprophytic in certain species of rats and does not as a rule, kill the animal.

Below is given a summary of experiments carried out with four different mercurial compounds on the *T. lewisi* experimentally inoculated in white rats.

#### DISCUSSION

At the outset it might be advisable to discuss the justification of regarding the action of medicaments upon trypanosomes in the experimental animal as criteria of their influence upon the spirochete in human syphilis. While the exact biological status of the spirocheta *pallida* has not been definitely fixed, the preponderance of scientific opinion is in favor of its being an animal parasite. Study of cultures of the spirochete under dark-field illumination on a warmed stage enables one to detect reproduction by longitudinal fission, which is an attribute ascribed to animal organisms. The parasite which we have, for the greater part, employed in our studies, is the *T. equiperdum*, the parasite of horse syphilis or "la dourine." This disease is contracted by horses through coitus and commonly leads to a fatal outcome with paralysis as a terminal symptom.

We have employed the spirochete of Obermeyer, the parasite of relapsing fever, in many of our tests and these organisms have been influenced by the same drugs that exerted an influence upon trypanosomes, and they have remained uninfluenced by the medicaments that were inert in their effect on trypanosomes.

Inorganic arsenic has no effect on experimental trypanosomiasis except in huge doses, and it has but a feeble effect upon the symptoms of human syphilis. Salvarsan has a remarkable sterilizing influence in experimental trypanosomiasis and effects a cure in the dose of 15 to 20 mg. per kilo of body weight. Salvarsan rapidly destroys the spirocheta *pallida* in living tissues when it comes in contact with the same. The prompt disappearance of the parasites in the chancre and in mucus patches is evidence of this action.

This parallelism in the effect of remedies upon trypanosomes in the experimental animal and their effect upon human syphilis cannot, however, be carried too far. We believe that we are justified in anticipating that a remedy which will exert a powerfully destructive influence upon trypanosomes *in vivo* will exert a similar influence upon the spirochete of syphilis, but the converse of this proposition is not of necessity true.

The failure of a chemical substance to influence trypanosomiasis does not indicate that it will be equally inefficacious in its effect upon the spirochete of syphilis. It must be remembered that infection of the white rat with the *T. equiperdum* produces an acute virulent disease which destroys the life of the animal in from 4 to 7 days. Within 24 to 36 hours after intraperitoneal injection with the blood of an infected animal, the trypanosomes appear in the circulating blood, increase in number from day to day until before death, there are more trypanosomes than there are erythrocytes. It is a severe test for a therapeutic agent, injected into the blood 24 hours after infection, to destroy the rapidly multiplying parasites. To accomplish this, a massive sterilizing dose must be administered. This is only possible with drugs of low toxicity such as salvarsan. Mercury cannot be given in sufficient dose because of its greater organotropism and consequent poisonous effect upon vital centers. None of the mercurial compounds in common use, are capable of destroying the trypanosomes nor of materially prolonging the life of the infected animal. Whether the failure of mercury to accomplish this result is due solely to its high toxicity or to lack of selective influence upon trypanosomes, cannot be definitely stated.

Syphilis is a disease in which certain defensive agencies of the body are brought into operation. The invasion of the blood stream is gradual, and even after the spirochetemic septiceemia takes place (during the so-called secondary period), protective influences are at work which destroy many of the parasites lodged in the tissues. If this were not the case, the chancre and the generalized eruptions would not disappear spontaneously as they commonly do. In some persons, particularly those in depraved health, the defensive bodies are weaker, and untreated, the early symptoms progress rapidly, and may lead to a fatal termination.

Syphilis ordinarily is a chronic disease and not an acute overwhelming infection such as is produced by the *T. equiperdum* or

the *T. brucei* in the white rat. Mercury, in syphilis, therefore, has a better opportunity, even in small doses, to exert an effect.

Several centuries of experience have taught us that mercury is a valuable drug in the treatment of syphilis.

From the foregoing the following propositions may be formulated:

(1) *The fact that a chemical substance is capable of destroying the T. equiperdum in experimentally infected animals is strong presumptive evidence of its ability to exert a favorable effect in syphilis.*

If this proposition is true and we believe it to be so, this laboratory method constitutes an excellent criterion for the comparative study of new drugs. Of course the actual effect of a remedy in syphilis can only be determined by its influence upon the lesions and the parasites of experimental syphilis, and by its effect on human syphilis.

(2) *The failure of a chemical substance to destroy the parasites in experimental trypanosomiasis is of itself no proof that the medication may not exert a favorable influence upon syphilis.*

Chicken spirillosis, due to infection with the spirocheta gallinarum, appears to be a less virulent disease than experimental trypanosomiasis (*equiperdum*) and European investigators have reported demonstrable effect upon these parasites by certain mercurial compounds.

#### THE EFFECT OF DRUGS IN VITRO AND THE INTERPRETATION OF THE RESULTS AS A THERAPEUTIC GUIDE IN THE TREATMENT OF EXPERIMENTAL INFECTIONS

By adding chemical substances in varying quantities to fluid cultures freshly inoculated with bacteria, one may determine the amount necessary to inhibit the growth of the organisms under consideration and ultimately destroy them. The *antiseptic* value of the chemical may be thus established. The *germicide* value may be determined by the U. S. Public Health or the Rideal-Walker methods, which have been detailed elsewhere.

Of the various medicaments which we have from time to time tested out on bacteria, none has hitherto equaled the bichloride of mercury and similar mercuric compounds. While the staphylococcus and the bacillus typhosus are readily killed in the test tube by mercuric chloride in great dilution, this drug will not destroy these bacteria in the living body.

This discrepancy may be due to three causes: the inability to ad-

minister a sufficiently large dose of mercury to animals without injurious and fatal effect on the body cells, the presence in the body fluids and cells of complex organic substances which may take up or change the mercury before it is permitted to attack the bacteria, and the lack of a specific affinity for the parasites.

Mercury is perhaps the best bactericide in the test tube that is known, and yet no notable results appear to have been obtained in human bacterial diseases by its use.

The effect of a drug on bacteria *in vitro* is no sure guide as to its action on the same germs *in vivo*.

The destruction of bacteria in the test tube is doubtless due to a biochemical union between the drug and the protoplasm of the organism, although some investigators argue that the action is brought about by adsorption, which is a physical process. In either event the specificity of the action is governed by selective affinity. This brings us to a consideration of the following interesting query: *Has salvarsan a greater selective affinity for the spirochete of syphilis than mercury?*

Let us first examine the laboratory data bearing upon this question. From the experiments already detailed it is seen that salvarsan has an enormously greater destructive influence upon the spirochete pallida in culture than has mercury. Mercuric chloride kills the spirochete according to an experiment carried out by us in the dilution of 1 to 100. Salvarsan destroys the spirochete in 1 to 10,000 to 1 to 100,000. We may therefore deduce that in the test tube salvarsan has a greater affinity for the spirocheta pallida than mercury.

As indicating that the parasiticide action is a selective one, we may refer to the fact that vegetable organisms such as the staphylococcus and the bacillus typhosus, are far more vulnerable to the action of mercury in the test tube than to salvarsan, although the latter is not devoid of germicidal effect. Our experiments with mercury and salvarsan on trypanosomes *in vitro* demonstrate that salvarsan is distinctly more parasiticide than mercury. In general terms it may be stated that *in the test tube salvarsan exhibits a greater affinity for animal parasites, and mercury a greater affinity for vegetable parasites.*

These laboratory results are rather in accord with clinical observation. While mercury doubtless for the reasons above referred to, has not yet been demonstrated to destroy vegetable parasites in the



living subject, salvarsan has accomplished this result in several diseases of animal parasitic origin. One need only refer to relapsing fever, yaws, syphilis, the tertian type of malaria and experimental trypanosomiasis.

*In vivo* it is true, the only disease in which mercury has achieved signal results is syphilis, a disease due presumably to an animal parasite.

Some writers have alleged good results with mercury in the treatment of leprosy, tuberculosis and pus infections, but these are not capable of scientific proof. The predilection of mercury for vegetable parasites *in vitro* suggests that when active mercurial compounds of sufficiently low toxicity are produced, such drugs may exert a curative influence in bacterial diseases.

Our test tube experiments in the laboratory all point to a greater selective affinity of salvarsan for *spirocheta pallida* than is possessed by mercury.

#### THE COMPARATIVE EFFECT OF MERCURY AND OF SALVARSAN IN EXPERIMENTAL TRYPANOSOMIASIS

From the tables set forth of the influence of mercuric chloride in experimental trypanosomiasis (*T. equiperdum*), it is seen that this substance has no demonstrable effect upon the parasites, even in sublethal doses. Mercury was administered intravenously by us also to animals infected with the spirochete of Obermeyer, the *T. lewisi* and the *T. brucei*, with the same negative influence. Salvarsan on the other hand in the dose of 15 to 20 mgs. per kilo of body weight, sterilizes animals infected with *T. equiperdum* and in adequate doses the other infections referred to. It might be argued that the difference in effect is merely owing to the fact that mercury on account of its toxicity cannot be administered in this dose. That the question goes beyond this is evidenced by the fact that doses of 3 to 6 mg. per kilo of salvarsan will keep the blood free of parasites for a number of days whereas a similar dose of bichloride of mercury has no such inhibitory effect upon the multiplication of trypanosomes and their appearance in the blood. *The superiority of the influence of salvarsan over mercury in experimental trypanosomiasis is incontestable.* This fact is a confirmation of the thesis that salvarsan has a greater affinity for animal parasites in the living body than has mercury.

ON THE POSSIBILITY OF PRODUCING NEW AND SUPERIOR COMPOUNDS  
OF MERCURY

The fact that mercury has a favorable influence upon the course of syphilis is established by several centuries of experience. The value of the drug is lessened, however, by its relatively high toxicity, and perhaps also by the fact that the inorganic salts of mercury and the organic compounds generally employed, have not sufficient selective affinity for the spirochete of syphilis. Salvarsan is tolerated intravenously by rats in the dose of 100 mg. per kilo of body weight; the bichloride of mercury cannot be borne in doses above 2 mgs. per kilo. It is seen therefore that mercuric chloride is 50 times as toxic as salvarsan. Salvarsan moreover has a greater selective influence on trypanosomes and spirochetes than has mercuric chloride, in doses weight for weight.

In elaborating salvarsan, Ehrlich used the sodium salt of arsanilic acid as the starting point. Atoxyl has a greater trypanocidal effect than inorganic arsenic, but is markedly inferior to salvarsan. There is every reason to believe that new organic compounds of mercury can be produced which will have a greater destructive influence on parasites than inorganic mercury, such as mercuric chloride. We have indeed prepared several organic mercury compounds which far transcend mercuric chloride in their effect on bacteria, and are likewise superior to this drug in their effect upon trypanosomes. Compound No. 99, prepared in our laboratory kills the staphylococcus in the test tube in a dilution of 1 to 5,000,000, whereas mercuric chloride accomplishes this result in 1 to 100,000. It is thus seen that in this test, compound No. 99 is fifty times more bactericidal than mercuric chloride. We have also demonstrated by tests on animals that this new compound is of lower toxicity than mercuric chloride, although we are not prepared to give the exact figures until more numerous repetitions of the test have been carried out. Compound No. 99 contains less mercury than mercuric chloride. Its increased germicidal and trypanocidal properties are to be attributed to the particular constitution of the molecule.

Our experience in chemotherapeutic work persuades us to believe that Ehrlich's working hypothesis concerning the existence of chemo-receptors in parasites, is correct. Ehrlich, for instance, regarded the presence of the hydroxyl ( $\text{O H}$ ) and amino ( $\text{N H}^2$ ) groups in salvarsan as of great importance. Experiments which we have

carried out on the arsenical series incline us to the view that the amino radical in salvarsan is perhaps as important as the arsenical group; the former appears to be necessary to enable the medicament to fasten itself to the parasite; this suggests the presence in the latter of amino receptors. Mercury can doubtless be combined with chemical substances in such a manner as to increase its affinity for parasites, both animal and vegetable. To be sure fruitful work along these lines requires infinite patience and an enormous amount of experimentation. Even after an ideal therapeutic mercurial compound is prepared, it must be of relatively low toxicity in order to be of practical value. And after these vital considerations are fulfilled, there are certain clinical desiderata which are of importance. The compound, if insoluble, cannot be injected intravenously, and intramuscular injections may be so painful as to render the product clinically ineligible. As a matter of fact, our compound No. 99 is so painful by intramuscular injection that its use by this method had to be abandoned. Fortunately it can be rendered soluble and used by intravenous infusion. It is being tried out by this method at the present time and if favorable results are obtained, due publication of its value in syphilis will be later published. It appears to us quite possible that compounds of mercury may be produced which may possess curative influence in bacterial diseases, for the affinity of mercurials for bacteria in the test tube is much greater than that of salvarsan.

#### CONCLUSIONS

1. The most valuable scheme for the determination of the bacterial properties of new compounds is by the correlated employment of the antiseptic and germicidal tests *in vitro* and by the use of the drug in experimentally infected animals.
2. The best method of determining the trypanocidal properties of new compounds is by the parasiticide test *in vitro*, the test *in vitro-vivo* and by the employment of the medicament in experimentally infected animals.
3. Our test in *vitro-vivo* has shown itself to be more delicate in the demonstration of the trypanocidal activity of chemical compounds than any other test. Animals infected with trypanosomes treated with mercuric chloride by this method, were for the first time kept sterile for a number of days, thus demonstrating some trypanocidal effect exerted by mercury.

4. The fact that a chemical substance is strongly germicidal in the test tube is no evidence that it will exert a demonstrable influence on the same organism in the living body. Such substances, however, are more promising for chemotherapeutic investigation than those which are inert.

5. Vegetable organisms such as the *staphylococcus aureus* and the *baecillus typhosus* are far more vulnerable to the action of mercury in the test tube than to salvarsan. Indeed, mercury possesses stronger bactericidal properties in the test tube than any chemical agent with which we have experimented.

6. Salvarsan, however, is not devoid of germicidal effect as it kills the *staphylococcus* in the dilution of 1 to 2000 upon prolonged exposure.

7. Salvarsan, in our experiments, has shown itself to be, by far, the most powerful trypanocide in the test tube known. By the method *in vitro-vivo*, it destroys trypanosomes in dilution as high as 1 to 40,000. Bichloride of mercury shows markedly inferior values in this respect. The superiority of the influence of salvarsan over mercury in experimental trypanosomes is incontestable.

8. In the test tube salvarsan exhibits a greater destructive influence on *animal parasites*, and mercury a greater destructive influence on *vegetable parasites*. Salvarsan is a powerful trypanocide and a feeble bactericide; mercury is a powerful bactericide and a relatively feeble trypanocide.

9. Trypanosomes and spirochetes appear to react chemotherapeutically in a similar manner. Medicaments which have a destructive effect upon the former, likewise appear to exert a similar influence upon the latter.

10. There is strong presumptive evidence that chemical substances which are capable of destroying trypanosomes in the animal body, exert a favorable effect in syphilis.

11. The failure, however, of a chemical substance to destroy the parasites in experimental trypanosomiasis is, of itself, no proof that the medicament may not exert a favorable influence in syphilis.

12. Our laboratory experiments on trypanosomes and spirochetes point to a greater selective affinity of salvarsan for the spirocheta *pallida* than is possessed by mercury.

13. Mercuric chloride has a much greater organotropic effect than

salvarsan; in our experiments mercury was 50 times more toxic for white rats than salvarsan.

14. A group of new organic mercury compounds has been prepared by us which far transcend mercuric chloride in their bactericidal power in the test tube. One new compound has shown itself to be over 30 times more powerful in this respect, both by the Rideal-Walker and the "antiseptic" test.

15. These new mercury compounds also exhibit a greater destructive influence upon trypanosomes than does mercuric chloride.

16. Some of these compounds have shown a lower toxicity than mercuric chloride.

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OBSERVATIONS ON THE BLADDER IN DISEASES OF THE  
CENTRAL NERVOUS SYSTEM.—AN ANALYTICAL  
STUDY OF 117 CASES

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OSLER once said, "That if one knows syphilis he knows medicine." This statement has a fitting application to diseases of the bladder, for we daily appreciate the extreme importance of recognizing syphilitic manifestations of this organ. The involvement of the neuromuscular apparatus consequent upon lesions in the central nervous system due to late syphilitic changes, is by far the most frequent, and certainly the most important, and will serve as the subject of this communication.

A year ago in the *Interstate Medical Journal*, 1916, vol. xxiii, No. 1, we reported an analytical study of fifty cases and called attention to certain changes in the bladder which are so constantly present in diseases of the central nervous system. At that time, we stated that we believed this picture to be pathognomonic of central nervous system disease. Since then we have studied 125 cases in which this bladder picture was invariably present. The records of 117 of these 125 cases are sufficiently complete to allow them to be tabulated. Believing firmly that this bladder picture strongly suggests neurological disease and realizing the lack of general appreciation of this phase of neurological urology, we feel that a presentation of an analytical study of these cases is seasonable.

As such a large percentage of disease of the central nervous system has as their initial symptom, disturbances of bladder function, and as so many surgical diseases associated with bladder disturbances

are either complicated by or associated with tabes, it is apparent how extremely important should be the recognition of this type of bladder. This bladder picture under reference has been commonly designated as the "tabetic bladder," evidently because it was supposed to be representative solely of tabes. Such, however, is not the case, as it is found in many other diseases of the central nervous system, and in individuals who have as yet been pronounced neurologically normal. Therefore, the term "tabetic bladder" seems a faulty one. It is for this reason that we have spoken of it as the bladder of central nervous system disease. We feel convinced that this picture is strikingly suggestive of neurological disease, even though in many cases our findings have not been confirmed by neurologists. On this account we have grouped our cases into 2 classes in order to compare the findings: those which have been neurologically confirmed as having definite central nervous system disease, and those which have not been so confirmed:

*Etiology.*—Of the 117 cases, there are 107 males, and 10 females. Average age, 45 years; oldest, 73; youngest, 22. One hundred and eleven are white, and 6 colored. It is of interest that there are only 6 colored patients. Tabes in the colored race is uncommon in this series; we have 3 definite tabetics; 3 unconfirmed. A case of lead poisoning gave the typical bladder orifice picture that is seen in central nervous system disease. Occupation seems to play no important role, except that many of the patients are laborers. This of course is to be expected, owing to the preponderance of clinic patients, there being 85 clinic and 32 office patients.

*Marital.*—Concerning the marital condition, a history of the patients having had children was obtained in 47 instances; 34 of these had children; 13 did not. Twenty-five per cent of the office patients had children; 30 per cent of the clinic patients had children. Eighty-two per cent of those having children, had two or more. Of the cases mentioned, 48 per cent were definitely specific or tabetic, with children. Twenty-eight per cent were unconfirmed cases, with children. Fifteen percent were in patients with a positive Wassermann or tabes, without children; 8 per cent were nonconfirmed patients, without children. In other words, almost twice as many of the patients with a positive Wassermann or signs of tabes had children, as those who had negative Wassermanns and unconfirmed tabes. On the other hand there were about twice as many of the specific or tabetic

individuals without children as the nonspecific without children. Also we note that 76 per cent of the specific cases had children against 24 per cent who did not. The proportion of well, sick and dead children coming from patients with a positive Wassermann, or tabes, bore the same relation as well, sick and dead children did to the nontabetic, or the patients with a negative Wassermann, whereas miscarriages were 8 times as frequent in the families of tabetics as in the nontabetics.

*Previous Diseases.*—Syphilis and gonorrhea occurred as the most frequent previous diseases. A history of previous syphilis was given in 50 per cent of the office cases and 41 per cent of the clinic cases, or 45 per cent of all. This lower percentage of previous syphilis in the clinic patients was taken entirely from the patient's given history. When we analyze our findings in these cases by studying their Wassermans, and signs of syphilis, we find that clinic patients also give 51 per cent, so that 50.5 per cent have had previous syphilis. Fifty-nine per cent of the definite neurological cases had positive blood Wassermans. Our statistics on spinal fluid analysis of tabetics and nontabetics, are not sufficient to be of any importance, as the unconfirmed cases were so infrequently sent into the hospital for spinal fluid analysis, and a great many of the tabetics, we find, had gone without this analysis. However, in this series we note from the number of neurological cases that have had spinal fluid analyses, 75 per cent were positive, 25 per cent were negative. One of the cord tumors was negative; the other one was not examined.

A history of previous gonorrhea was given in 50 per cent of the cases; 15 per cent had had no previous venereal history. Rheumatism, typhoid fever, malaria, smallpox, mumps, chaneroid, pneumonia, and bronchitis were mentioned among the previous diseases.

A history of chanere was obtained in 30 per cent of the private patients and 30 per cent of the clinic patients. There was a definite history of secondaries in 24 per cent of the cases; 8 per cent of the patients gave a history of definite chanere without secondaries; 22 per cent gave a history of chanere with secondaries. There were four patients with a negative chanere history, but positive secondaries, or 8 per cent. Of the patients giving a history of lues, 48 per cent had received treatment for lues, but the majority had received very inadequate treatment. "Pills for a few weeks," or "rubs for a short time," had been the most frequent treatment.



*Previous Diagnosis.*—Previous diagnosis was mentioned 73 times. Tabes was diagnosed previously in 25 per cent; bladder or kidney trouble had been given in 29 per cent. This is quite striking and shows the frequency of bladder symptoms in these cases. Neurasthenia, 10 per cent, rheumatism and sciatica, 10 per cent; prostatitis, 8 per cent; stomach and intestinal trouble, 12 per cent. The gap was filled by such diagnoses as malaria, tuberculosis, pelvic trouble, multiple sclerosis, etc.

*Present Diagnosis.*—Our diagnosis on admission: Definite neurological disease, such as tabes, cerebrospinal lues, post-apoplectic conditions, spinal cord tumors, paresis, etc., occurred in 46 per cent of the series. Of this number, the diagnosis was made in the urological clinic in 46 per cent, and by the neurologist in 54 per cent; 46 per cent of the cases diagnosed by the cystoscope were confirmed by the neurologist and 54 per cent were not. Of the 54 per cent of unconfirmed cases, 6.2 per cent were later confirmed, these being 2 spinal cord tumors, and a case of paresis; the remaining 48 per cent of the cases were associated with prostatitis, prostatic hypertrophy, bladder tumors, renal calculus, calculus pyonephrosis, paralysis agitans, lead poisoning; and as yet have not been neurologically confirmed. It is this group which is of particular interest to us because the bladder picture and other associated diagnostic phenomena are as pronounced and definite as they are in the confirmed tabetics. This class will be thoroughly watched and neurologically overhauled at frequent intervals.

*Diagnostic Symptoms and Findings.*—Throughout our analysis we have noticed such a close similarity between office and clinic patients, with reference to various symptoms and findings, that we will not separate the two groups, but will aggregate them with their general average. The average duration of symptoms was  $5\frac{1}{4}$  years; the longest, 26 years, shortest, 2 years.

*Urinary Symptoms.*—Mentioned in 111 patients, or 95 per cent. Of these, 95 per cent had urinary symptoms, and 5 per cent presented no urinary symptoms. Of the 5 per cent without urinary symptoms, one-half occurred in association with definite disease of the central nervous system; the other half in cases unconfirmed.

*Frequency of Urination.*—Frequency of urination occurred in 58 per cent of the cases. Fifty-four per cent of the nontabetics had frequency, and 46 per cent of the tabetics had frequency.

*Incontinence.*—Incontinence of urination occurred in 34 per cent of all; 68 per cent of these patients with incontinence were definite tabetics. One of the cases with incontinence of urine, in which we diagnosed nerve disease by the bladder picture and which was not confirmed by the neurologist, later proved to have a spinal cord tumor. Our findings were confirmed by autopsy.

*Obstruction to Urination.*—Obstruction to urination occurred in 36 per cent of the cases; 62½ per cent of these patients suffering with obstruction to urination had definite neurological disease; the other 37½ per cent were not confirmed. In this series of obstruction cases, one case that had been previously pronounced neurologically negative, later was proved to have paresis.

*Pain, Burning and Urgency* were present in 37 per cent.

*Sexual Powers.*—One of the most uniform and important findings throughout our analysis has been the disturbed sexual capacity, particularly in disease of the central nervous system. It has frequently been the initial symptom. The analysis of this series shows that in tabes, and in other central nervous system diseases, the sexual powers were either completely lost, or disturbed in 82 per cent; they were given as normal in 18 per cent. Of the series of cases not confirmed, but showing the characteristic picture at the bladder neck, 48 per cent had disturbed sexual power, and 52 per cent had no disturbance. There is quite a disproportion between the confirmed neurological and unconfirmed with reference to their disturbed sexual powers. However, when we consider that 50 per cent that were not neurologically confirmed have disturbed sexual powers, it makes us cautious as to our prognosis, and should stimulate observation. We thought it would be of interest to tabulate the cases which presented sexual disturbances, and urinary disturbances with positive or negative Wassermann in the confirmed and not confirmed cases. Such an analysis shows the following: Patients with definite central nervous system disease, who presented sexual disturbance and urinary disturbance, and a positive Wassermann, 30 per cent; the same group with sexual disturbance, urinary disturbance and negative Wassermann, 40 per cent; of the unconfirmed with sexual disturbance, urinary disturbance, and positive Wassermann, 4 per cent; this same group with sexual disturbance, urinary disturbance, and a negative Wassermann, 26 per cent. Therefore, we see that the tabetics with such symptoms have about an equal chance for a positive and negative Wassermann.

In the cases which are not confirmed, the negative Wassermann is to a positive Wassermann as 6 is to 1. It is possible, however, that the 4 per cent of cases having a positive Wassermann may be the ones who may shortly develop general neurological disease. A striking fact is that the patients who have had disturbed urinary symptoms with normal sexual symptoms have seldom been confirmed. This emphasizes the importance of sexual derangements.

*Pain.*—Pain was present in 75 per cent of the cases which were mentioned. This includes pains commonly associated with tabes, and those referred from pelvic diseases. Of this percentage, 65 per cent occurred in tabetics; 35 per cent in nontabetics, but 93 per cent of the tabetics had pain and 87 per cent of the nontabetics had pain. The commonest location of pain in the tabetics was in the legs, it being 50 per cent; next commonest in the back, 35 per cent. In the non-confirmed cases, 61 per cent had backache; 50 per cent pain in the legs. Many of the cases, of course, have a combination of backache and leg pains. Suprapubic pain, pain in the scrotum, were about equally divided between the two groups.

*Uremia.*—We have been impressed with the great number of uremics in this series. It has been our impression for a long time that the cases of tabes which showed the most improvement under treatment, were those which were associated with uremia, whereby the improvement in the patients uremic condition led greatly to the restoration of his general health. We believe that our impression has been a justifiable one and will be confirmed by our findings in this group of cases. That is to say, that many of the symptoms and toxic conditions which are suffered by patients with central nervous system disease, are undoubtedly due to the uremia. For we have seen quite a number of patients in this series who were extremely pale, weak, and toxic, who had been considered to be in this deplorable condition on account of their nervous system entirely, who have wonderfully improved, and in several instances almost entirely relieved of symptoms by drainage, and measures to relieve their profound uremia. Uremia was mentioned in 69 cases, 29 were definitely uremic, or 42 per cent; 40 were not uremic, or 58 per cent. Of the 42 per cent who had uremia, 86 per cent were in patients with central nervous system disease; 14 per cent occurred in cases, which were not neurologically confirmed. This shows a very high percentage of uremia occurring in the definite neurological cases. The latter group with uremia has

been of interest, because one case had the typical bladder picture, a negative Wassermann, a high residual urine, marked uremia with no evidence of a mechanical obstruction and died of his uremia. It is possible that if we could have treated this patient earlier, and spared him of his renal injury, he may have lived long enough to have shown evidence of nervous system disease. There were 40 cases that did not have uremia, or 58 per cent; of these 11 were tabetics, or 27½ per cent; 29 nontabetics, or 72½ per cent.

*Hematuria.*—Seventeen and one-half per cent of the cases had a history of hematuria. Of these, 1/3 were tabetics, and 2/3 were nontabetics. The nontabetics usually gave a history of terminal hematuria of deep urethral origin. There have been two very interesting and profuse hemorrhages, associated with vesical crises, occurring in tabetics. The bleeding seemed to have come from the deep urethra, and was controlled with adrenalin. One of these patients had repeated attacks. These hemorrhages occurring in tabetics are quite out of the ordinary and hard to control. Another case in this series bled to death from a small incision into the kidney for drainage, showing absolutely no power of clotting, probably due to vasomotor disturbance.

*Examination of External Genitals.*—Examination of the external genitals shows them to be somewhat atrophic and flabby, in the majority of cases. Varicocele is frequent. We have noticed spasm of the anterior urethra four times, occurring twice in tabetics and twice in nontabetics; that is 3.7 per cent of the tabetics has a spastic anterior urethra, and 3.2 per cent of the nontabetics.

*Urine.*—Thirty-two per cent of all the cases mentioned had infected urines, 21 per cent were tabetics; 11 per cent unconfirmed cases; 68 per cent of all the cases were not infected, 31 per cent were in tabetics and 37 per cent in the unconfirmed. Furthermore 40 per cent of all the tabetics had infected urine, and 60 per cent of the tabetics did not have infected urine. Of the unconfirmed cases 14.5 per cent had infected urine; 85.5 per cent were clean. The infections were almost entirely due to the colon bacillus group; a very small percentage of the tabetics were gonorrheal.

*Presence of Prostatitis.*—Eighty-eight and one-half per cent of the patients mentioned had an associated prostatitis and seminal vesiculitis; 11.5 per cent did not; 50 per cent or an equal proportion occurred in tabetics and in those not confirmed. There were 10 cases

of prostatic hypertrophy associated with this picture; of these, 4 were confirmed tabetics, and 6 occurred in those patients who were not neurologically confirmed as having central nervous system disease. This is very important indeed, and serves to emphasize the importance of thorough cystoscopic investigation before removal of the prostate gland, for what appears to be definite prostatic obstruction by the history and rectal findings, since 3 per cent of this whole number of cases showed that tabes and prostatic hypertrophy occurred together, and 8.5 per cent occurred in definite central nervous system disease. We are convinced that many of the unfavorable results following prostatectomy, we speak particularly of incontinence, are due to the fact that the prostate was removed from patients suffering from some central nervous system disease. There are still clinics which do not advocate cystoscopic investigation as routine in prostatic surgery. If for no other purpose, the detection of a latent tabes by the cystoscope, would make such an investigation worth while, and we urge the profession to always make a careful cystoscopic examination, and pay attention to this bladder picture before attempting prostatic enucleation.

*Cystitis and Trigonitis* occurred in 22 per cent of the cases.

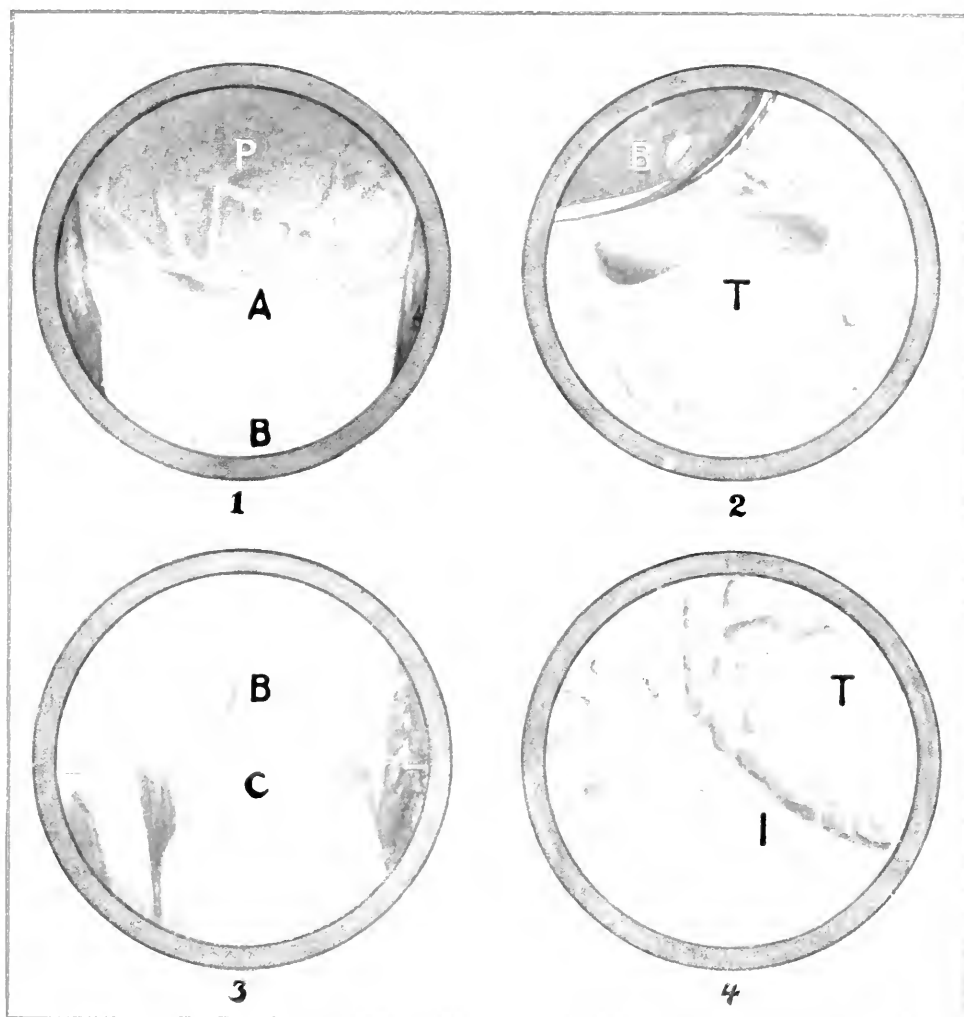
*Associated Conditions.*—There were four cases of bladder tumor associated with this bladder picture, 3 were carcinoma, 1 papilloma. One of the cases of carcinoma of the bladder occurred in a definitely confirmed tabetic, this case bled more freely than the average carcinoma of the bladder and practically bled to death; the others occurred in unconfirmed cases; one case had a small tumor at the dome of the bladder, which was removed suprapubically, and very easily, but the patient's convalescence was out of the ordinary to the amount of surgery; the other patient had a large carcinoma at the dome of the bladder with a violent alkaline cystitis. This case was of interest because the patient died of spontaneous rupture of the bladder in the region of the carcinoma. The papilloma was cured by intravesical high frequency applications. Other associated conditions were: 1 bladder calculus, which was removed by litholopaxy; one diverticulum of the bladder; 3 strictures of the urethra; 3 cases of calculus pyonephrosis, and one case of renal calculus. One of the cases of calculus pyonephrosis demanded drainage on account of an extensive infection, and promptly died. Tabetics have such an astounding lack of resistance that surgical interference is always grave, and usually contraindicated. The other

cases of calculus pyonephrosis have been kept in good condition by catheter drainage of the renal pelvis.

*Rectal Sphincter.*—The rectal sphincter was relaxed in 90 per cent of the cases mentioned; of these, 54 per cent were in patients suffering with disease of the central nervous system, and 46 per cent were in the unconfirmed. It was of normal tone in 7 per cent. Of this 7 per cent, it was four times as frequent in the nontabetic as it was in the tabetics. It was spastic in one tabetic, 3 per cent of the whole number of cases. Even counting those in which no note was made as to the rectal sphincter, 44.5 per cent had relaxed sphincters. This seems to be one of the most common and important findings. Associated with the relaxation of the rectal sphincter, there is usually a ballooning of the rectum.

*External Vesical Sphincter.*—The external vesical sphincter was spastic in 57 per cent of the cases mentioned. Seventy-one per cent of these were tabetics; 29 per cent in the unconfirmed. It was of normal tone in 43 per cent of the cases mentioned; 20 per cent tabetics; 80 per cent nonconfirmed. In the tabetics and definitely confirmed neurological cases 81 per cent were spastic; 19 per cent were not. In the nonconfirmed cases 33.3 per cent were spastic, and 66.6 per cent were not.

*Catheterization.*—On introducing the catheter, one generally meets an obstruction at the bulbo-membranous juncture. When the catheter passes through this external sphincter spasm, urine immediately flows, as the posterior urethra and bladder form a common cavity. This is quite different from the findings on catheterization either in cases of prostatic hypertrophy or prostatic cancer. In prostatic hypertrophy, of course the catheter does not obtain urine until it is inserted for a considerable distance, and then suddenly jumps over the lobe and urine is ejected; in prostatic cancer the spasm is frequently met in the same place as in the so-called tabetic bladder, but instead of urine coming immediately, the resistance is continued through the prostatic urethra and urine does not come until the internal sphincter is catheterized. Along with weakness or paralysis of the internal sphincter of the bladder, the detrussor or bladder musculature is in many cases usually weakened and considerably atonic. Forty-seven per cent of the cases mentioned had a normal detrussor musculature, and 53 per cent were weak. Eighty-two per cent of the weak detrussors occurred in tabetics, and 18 per cent in the unconfirmed, but 78



DRAWINGS FROM CYSTOSCOPIC EXAMINATION OF CASE 117.

- Fig. 1.—*A.* Internal sphincter muscle.  
*B.* Floor of urethra.  
*P.* Bladder wall, showing trabeculation.
- Fig. 3.—*B.* Floor of urethra.  
*C.* Verumontanum, showing orifice of utricle.  
*L.* Lateral urethral walls.

- Fig. 2.—*B.* Air bubble.  
*T.* Trabeculation at dome of bladder.

- Fig. 4.—*I.* Tip of trigone, showing elevation and fan-like appearance of trabeculation.  
*T.* Trabeculation.

(Caulk-Greditzer: Observations on Bladder.)





per cent of the tabetics had weak detrussors, and 22 per cent were normal. Twenty-one per cent of the unconfirmed cases had weak detrussors, and 79 per cent normal. It is again this series of unconfirmed cases with weak detrussors that we believe demand vigilant observation.

Before giving the statistics concerning the findings of the interior of the bladder and internal orifice, we wish to briefly describe the typical cystoscopic picture, which we believe is representative of central nervous system disease. The most constant and striking finding is the appearance of the internal sphincter. With the cystoscope in its normal horizontal position, there is a feeling of relaxation, which one does not get in normal cases. On observing the sphincter margin it has usually been found to be without striking appearance above and laterally, but as one approaches the floor, it is observed that immediately the striæ of the floor of the urethra can easily be seen external to the sphincter. On depressing the eye piece of the cystoscope and withdrawing the instrument, the posterior urethral floor or the supramontane urethra may be inspected, showing its folds, and the gutter appearance of the urethra, and the lateral urethral walls (Fig. 1). Very frequently the scope may be withdrawn, and the verumontanum (Fig. 3) brought plainly into view, the orifices of the utricle and ejaculatory ducts may be inspected. This, of course cannot be done in the normal urethra, for the reason that, with normal tone, the musculature clamps so closely to the lens that inspection of the urethra is impossible. Such urethras are usually very insensitive and seldom require local anesthesia for examination. Associated with this orifice picture, the trigone (Fig. 4), is usually elevated, but seldom husky and hypertrophic, as behind mechanical obstructions; the interureteric bar is usually lifted and thin. Laterally the trigone at its tips frequently fans out into trabeculæ, which spread out over the lateral walls of the bladder. The ureteral orifices have shown nothing in particular, except that in some cases they have been sluggish in their ejaculation of urine. With this picture of relaxation at the internal orifice of the bladder, there is usually bladder trabeculation. This trabeculation, we have found is usually a general trabeculation (Fig. 2), and offers no particular characteristics, except that possibly it may be a little more delicate than trabeculation seen back of mechanical obstructions. Koll believes that it has a predilection for the lateral fornices, and has a specific appearance, but our cases have not

been so definite in this respect, as they have all been more or less generalized, and have assumed various grades of trabeculation.

*Internal Sphincter and Verumontanum.*—In analyzing our cases, we find that the internal sphincter was relaxed in 98 per cent; 2 per cent were spastic. Of the relaxed group, 78 per cent had sufficient relaxation to allow cystoscopic inspection of the verumontanum; 20 per cent did not show sufficient relaxation to allow this inspection. Of the 78 per cent with marked relaxation, 50 per cent of these were tabetics, and 50 per cent were in cases not confirmed, and 80 per cent of the tabetics had sufficient relaxation to allow the verumontanum to be visible; 20 per cent did not. Seventy-five per cent of the unconfirmed cases were sufficiently relaxed to show the verumontanum; 23 per cent were not; 2 per cent were spastic. It is again striking how closely parallel the proportion of tabetic and nontabetic percentages run with reference to the dilatation of the internal sphincter. This finding, above all seems to be the one typical, and by far the earliest in many cases of central nervous system disease. By appreciating this picture we have in numerous instances diagnosed lesions of the central nervous system by means of the cystoscope.

*Trigone.*—The trigone was elevated, that is, showed signs of hypertrophy in 64 per cent of the cases studied. Of this percentage of cases showing elevation, 63 per cent were cases with central nervous system disease, and 37 per cent were not confirmed. It was mentioned as normal or congested in 36 per cent. Of this percentage, 38 per cent occurred in neurological disease, and 62 per cent in the unconfirmed group. It is observed also that 75 per cent of the tabetics had elevated or veiled trigones, and 25 per cent normal ones. Of the unconfirmed cases, 50 per cent were elevated or hypertrophied and 50 per cent were not.

*Trabeculation.*—Trabeculation was mentioned in 100 cases; it was present in 94 per cent and absent in 6 per cent. Of the 94 per cent which showed trabeculation, 53 per cent were tabetics; 47 per cent nontabetics. Of the cases in which it was absent, 33.3 per cent were tabetics; 66.6 were nontabetics. On the other hand trabeculation was present in 96 per cent of the patients with diseases of the central nervous system; trabeculation was absent in 4 per cent of these cases. This high percentage of trabeculation in tabetics stamps it in our estimation as a very important physical finding. Trabecula-

tion was present in 92 per cent of the unconfirmed cases, and it was absent in 8 per cent of these cases. Therefore, with a finding so constant in disease of the central nervous system, and equally as constant in the unconfirmed, its presence certainly creates suspicion in the latter group of cases. We are greatly interested in following this series of cases. As to the location of the trabeculation, 80 per cent was found to be general, that is on the base, lateral wall and dome; and only 20 per cent occurred on the base alone. These percentages were equally shared by the neurological and nonneurological. We have been able to study 13 cases in which there was a relaxation of the internal vesical sphincter, not sufficient to show the verumontanum and associated with a relaxed rectal sphincter; of these cases, again about 50 per cent occurred in definite central nervous system disease, and 50 per cent in the unconfirmed; 7 were the former; and 6 were the latter. All of the cases with central nervous system disease in this series had trabeculation associated with the relaxation, and 4 of the 6 had trabeculation in the unconfirmed. There were four patients in whom the bladder sphincter was relaxed sufficiently to show the verumontanum, but the rectal sphincter was not relaxed; 2 of these were in tabetics and 2 were in the unconfirmed cases.

*Functional Test.*—Phenolsulphonphthalein has been used throughout this series to the exclusion of all other dye tests. There has been a delay in the time of appearance and a diminished output almost invariably proportionate to the amount of residual urine. Most of the tabetics without high residual urine, and the majority of unconfirmed cases have had practically a normal phthalein output.

*Endoscopy.*—It is found to be very difficult to keep the endoscopic field dry, as urine seems to be ejected directly from the ureteral orifices into the posterior urethra and over the verumontanum, so that during the examination of the posterior urethra, the operator is kept busily engaged constantly swabbing urine from the field unless the patient's buttocks are highly elevated.

*X-Ray Findings.*—We have made cystograms with thorium, collogol, argyrol, etc. These bladders were frequently filled in the clinic and patients allowed to walk up several flights of steps to the x-ray department. As we mentioned in our previous paper, we were quite surprised to find that we did not get a funnelling of the

internal vesical orifice. In most of these cases the cystograms showed clean cut lower boundaries. Recently, we have had several cases, however, in which there was a definite funnel shaped bladder orifice as shown by the cystogram. It is surprising that it has not occurred more frequently since the Johns Hopkins Clinic has observed it quite commonly. There has been one observation in particular, which has been of interest to us in several recent cases, and that is, if the patient's bladder is filled with solution and a comparative plate is taken with the patient lying and standing up, it is noticed that in tabetics, there is a dropping down or sagging of the bladder, and a toppling over forward. This does not occur in normal individuals. This is probably due to the marked relaxation of the various bladder and prostatic supports, namely the ligaments and muscular supports in this region. This, we believe, has not been previously demonstrated.

We have made a careful study of this series of cases in order to determine whether the neurological or the urological clinic made the diagnosis first. In cases with definite central nervous system disease the neurological clinic made the diagnosis first in 65.4 per cent of the cases; in the office the neurologist made the diagnosis first in 46.1 per cent, or an average of 55.8 per cent. In the clinic the diagnosis was made first by the cystoscope in 30 per cent of the cases, and in the office 46.1 per cent, or an average of 38 per cent. The diagnosis was made first by the cystoscope and not confirmed by the neurologist, but later confirmed by the neurologist in 6.2 per cent in the clinic. In other words, almost 50 per cent of the patients suffering with disease of the central nervous system, may have as their initial symptom disturbance of bladder function, such as frequency, dribbling and the like. It is extremely important for the urologist to recognize this picture. This high percentage certainly gives the cystoscope an important place as a diagnostic aid in diseases of the central nervous system. As 6.7 per cent of the 50 per cent which were not confirmed have been subsequently confirmed, and this percentage within a year, it should certainly make us appreciate the importance of this bladder picture.

*Treatment.*—General treatment embodies the proper care in hygiene and diet in an attempt to keep the physical condition in as good shape as possible; careful attention to the bowels and tonics are

indicated; urinary antiseptics, particularly urotropin in good size doses are given as routine. Cases with positive Wassermann reactions are treated in the neurological clinic with specific remedies. The tendency at present, however, is to use less specific remedies than formerly. In this group at least, we have noticed no more improvement in the patients who were treated with mercury, salvarsan, etc., than in the ones who have not been treated by these measures.

*Local Treatment.*—Our particular interest concerns the local treatment of these poor unfortunates. As far as their vesical condition is concerned they have frequently passed unnoticed and neglected, even those, in extreme, with bladder overflow have had their bladders treated only through pity. After our experience in handling this series of cases we are firmly convinced that an enormous benefit can be given these individuals and many of them can be made entirely comfortable; some of the patients with early involvements can be practically relieved of every bladder symptom.

The method of treating such bladders varies according to whether or not there is residual urine. The early cases without residual urine are treated with the idea of relieving their irritability and keeping them clean, and training them to exercise their weakened and lagging musculature, by regular attempts at urination; by practicing stopping and starting the urine at frequent intervals during each act. The idea of this, is in the first place to keep the bladder as empty as possible, and to prevent overstretching the already weakened musculature of the bladder; and in the second place to exercise what muscle fibers have remained uninjured, with the idea of strengthening them, so as to make evacuation more complete. Treatment of these cases is very similar to the treatment of chronic posterior urethral infections—namely, massages, dilatations, instillations and applications to the urethra. It is extremely important that the highest degree of asepsis be observed in any manipulation on these individuals. After repeated treatments to this class, we believe that we can truthfully say that we have seen but very few infections, and these only temporary.

Patients with residual urine, whether infected or not, are treated in a similar manner to the other group, but in addition, with systematic daily catheterization and irrigation. The infected bladders and, in many cases, kidneys, have universally improved and fre-

quently been made clean. Those individuals with residual urine who were not infected on admission have in several instances, even after scrupulous asepsis, become infected, but such infections have been mild and temporary, and have promptly cleared up, the residual urines having invariably lessened and in many instances entirely disappeared, so that patients, who had been previously bothered with constant dribbling of urine, have been made to urinate quite naturally without incontinence. We know of no more appreciative patients in the world than this class. Two patients in particular who had good-sized residual urines several years ago, and who were bothered with incontinence, at present empty their bladders completely and do not have the slightest incontinence. These cases, of course, are exceptional, but we are confident that if we had not in the beginning catheterized them regularly and released their bladders from distention, which is an important factor in depleting the muscle fibers which remain, they would have been dribblers at the present time.

About 80 per cent of the tabetics suffering with uremia have markedly improved by drainage. This type of case has improved much more than the tabetic with the same degree of nerve involvement without uremia, so that we are convinced that it is the uremia plus the tabes in many cases, that makes these individuals so pitiful. And it is this feature in the treatment of the tabetics that has been so surprisingly neglected.

In the face of the comforting results which we have seen, we hope that the profession will appreciate that bladders of these paralytics need attention and that surprisingly good results may be obtained by systematic treatment.

In closing, we are confident that a diagnosis can almost always be made of tabes and spinal cord disease by the cystoscopic picture of the bladder—in many cases before any other lesion becomes manifest. For in this series this characteristic picture was observed in three individuals who had been given a negative neurological examination, and who later were definitely confirmed; 2 were spinal cord tumors, one confirmed at autopsy, the other by operation; the third was a case of paresis. Furthermore, we trust that the deplorable neglect in the treatment of the paralytic bladder will cease to be so universal,

and that these individuals will be given the advantages of treatment as well as any other class of patients.

*Mortality.*—Of the 117 cases tabulated, 7 have died. Of these, 2 were tabetics; 1 a spinal cord tumor; the other 4 unconfirmed cases, or practically 6 per cent mortality. This mortality has been contributed to chiefly by renal insufficiency, as the cord tumor and one tabetic died of uremia, and 3 of the unconfirmed cases died of uremia; one of the tabetics died suddenly of collapse, after being comparatively in good condition. One of the unconfirmed patients died of ruptured bladder from carcinoma.

## SUBCONJUNCTIVAL INJECTIONS OF SALVARSANIZED SERUM IN THE MANAGEMENT OF OCULAR SYPHILIS

BY ROBERT SCOTT LAMB, M.D., WASHINGTON, D. C.

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SOME ten years ago in a paper read before the Medical Society of the District of Columbia, I strongly urged the use of subconjunctival injections of normal salt solution in diseases of the eyes; for after having tried many various kinds of medicated solutions in different strengths, as advocated by one or another ophthalmologist, and observed their action together with the reaction obtained, I had come to the conclusion that my results with normal salt solution were the best—at least for my use and probably for others.

I insisted it be given a place in the armamentarium commensurate with its value and that none condemn it without a fair trial.

No wonder then that I so gladly accepted the suggestion of my friend, Dr. Seibert, as stated in my paper written in 1915, to use salvarsanized serum as prepared according to the Swift-Ellis method and in use as an intraspinous injection by serologists and syphilologists.

Accordingly more than one hundred cases with ocular diseases of syphilitic origin, checked by Wassermann test, were treated with subconjunctival injections of salvarsanized serum and a brief report of results made before the Medical Society of the District of Columbia.

It was my intention to make an elaborate and tabulated report at some later date to one of the National Ophthalmologic Societies. However, time and opportunity have not been found so to do. Besides which I found that the report (brief as it was) I had made was rather generally approved and the use of the serum inaugurated by some ophthalmologists throughout the country with reasonable satisfaction to both patient and surgeon.

Unfortunately, as is well known, the problem of obtaining salvarsan made it difficult to carry on the treatment continuously and I attempted to use serum derived from the blood of those who had been injected by the preparations of an allied nature with good results but with greater irritating reactions and not such rapid resolution of the chemotic conjunctivæ. It was therefore a relief when the



conditions of the drug distribution changed so that our hospitals could get medicine of the original kind and enable us to use the serum.

The results have been quite as satisfactory as I was led to believe from my experience with the serum, as stated in my communication made May 23, 1915, and it gives me pleasure to recommend again its use subconjunctivally on the strength of another year and a half's experience with it.

The diseases most commonly found in the patients coming under observation and upon whom the serum was used were—iritis, iridocyclitis, keratoiritis and interstitial keratitis.

Two neuroretinitis cases showed marked response in much shorter time than usual, and whereas the treatment was used conjointly with intravenous salvarsan and Swift-Ellis spinal injections, nevertheless much credit is attributed to the subconjunctival injections for the return of vision to distant vision of 6/4 and J. 1. at 15 inches without glasses, when one eye of one patient on first examination showed no correct vision at any distance for direct vision and only indistinct object vision and L. P. peripherally. As he expressed it he could see a light by looking sidewise at it.

Perhaps it would be well to quote for the benefit of those wishing to obtain the serum the directions for its preparation.

“A dose of salvarsan or allied material is given intravenously in the usual manner. At the end of an hour, 50 or 60 or even 100 c.c. of the patient's blood are drawn by means of venous puncture; clear serum thus separated, allowed to stand an hour, then centrifugalized, is diluted to 40% with normal salt solution, heated to 56° C., for half an hour; then either hermetically sealed in ampules or kept cool until the following day, when it is put in ampules, capacity 1 c.c., and kept on ice a reasonable length of time, to be used whenever needed.”

Unfortunately handicapped as we are in being unable to obtain without restriction a sufficient quantity of the original material for intravenous injections, our investigations on a large scale must await the end of hostilities abroad, when it can be more satisfactorily demonstrated to any incredulous among us that subconjunctival injections of salvarsanized serum are worthy of premier place in the treatment of diseases of the eye due to syphilis.

## GUMMA OF THE NOSE.—A CLINICAL NOTE

BY THOMAS J. HARRIS, M.D., NEW YORK CITY

(Received for publication, December 6, 1916)

THE protean character of syphilis is one of its most characteristic properties; both textbook and clinical experience are constantly impressing this upon us. In spite of this fact the keenest observer at times may be deceived. Particularly true is this as applied to manifestations of syphilis in the nose.

The history of the following case illustrates this in a striking degree.

Miss X, age 25, presented herself in the summer of 1915 complaining of inability to breathe through the nose. There was no pain, no discharge. She had always been well. Patient was a well nourished young woman, free from external blemishes. There is a history of one sister having died of tuberculosis, and a second suffering from that disease for the last eight years. Physical examination was negative. Examination of the nose showed the right nostril almost completely obstructed by what appeared to be an enlarged inferior turbinal. It was possible to reduce this to a limited degree only by the use of cocaine and adrenalin. It was not sensitive to touch and did not bleed easily. A probable tubercular lesion was suspected. Local treatment was instituted with relief to breathing, and the patient discontinued treatment. One year later she presented herself complaining that all the symptoms of the year previous had returned with increased severity, and that she could not rest at night on account of the difficulty in breathing. There was a history of having been subjected recently to a severe physical and mental strain as a possible cause. Appetite was poor, and there was a slight reduction in weight. Examination of chest was again negative. Examination of nose showed a condition similar to what was found the year previous. The right side was almost completely obstructed by a smooth symmetrical swelling springing from the inferior turbinal anteriorly. The middle turbinal could not be seen. Upon the septum midway back on the left side a small mass was to be seen. The mass was pinkish in color, free from all ulceration, non-vascular and could be reduced only partially by astringents. Local treatment was instituted with gradual relief. For this purpose the galvanocautery was employed. Instructions were given as to measures for the general health. Treatment was continued until we left for our vacation the first of September. When we returned we found that the improvement in the breathing had been maintained. The nostril was now patulous in its lower portion. Behind the point where the galvanocautery had been applied, a nodular mass was to be seen.

It was decided to remove this with the cold wire snare. This was done, and the growth sent to the laboratory for examination with the opinion still unchanged that we were dealing with manifestation of nasal tuberculosis. To our surprise and chagrin the report came back that it was a gumma. A careful physical examination was then instituted to discover other lesions of syphilis, but none was found. An examination of the blood showed a positive Wassermann. Later a history was obtained of a primary lesion dating back from five to seven years. Salvarsan completed the cure of the nasal condition.

Gumma of the nose is a comparatively rare manifestation as met with by the rhinologist. We have kept no accurate records of our cases, but we recall only four that we have seen in recent years. Necrosis of the septum and turbinates as a result of either the breaking down of the gumma or of the deep ulcer is a far more common observation. Because of the location, it is free from the irritation which gumma of the mouth is exposed to. In consequence it can remain unaltered in character for an indefinite period, as occurred in the case just reported. It is wont to involve either the inferior turbinal or the septum. The growth may be solitary although it is frequently, as in this case, multiple. Its appearance is so characteristic that only its apparent innocence can explain a failure to recognize it. It may be described as a round smooth tumefaction covered by a mucosa of the usual color. Bosworth<sup>1</sup> speaks, however, of it as occasionally presenting a "bleached appearance due to a stretching of the covering membrane," and in other cases that there may be a "deep venon injection giving rise to a reddish or purplish hue." When the inferior turbinal is involved it is to be distinguished from a simple hypertrophy by the fact that it does not yield so readily to pressure or cocaine. If the growth is situated far back in the nose it may be difficult of recognition. Pain is not a prominent symptom, although there may be a complaint of deep-seated pain over the bridge of the nose. The differential diagnosis where the septum is involved is to be made from a deflection, ecchondroma, or exostosis, and from sarcoma and angioma, as well as from a possible tubercular infiltration. Deflection of the septum can be easily ruled out because of the absence of a corresponding cavity on the opposite side. The probe will show that the growth is neither cartilaginous nor bony. It can be, however, confused with sarcoma as the appearance of the two tumors is in some cases not unlike. Sarcoma, however, is apt to bleed, and is more extensive in its development. A microscopic examination may be required to definitely decide.

A tubercular swelling or tumor in the nose is an exceedingly rare condition. Lockard<sup>2</sup> in his recent book on Tuberculosis of the Nose and Throat was able to collect only forty-two cases in the literature. The growth may be primary or secondary, if we understand by primary that a careful search is necessary to reveal tuberculosis elsewhere. The tubercular infiltrate is wont to break down rapidly. When ulceration exists, a diagnosis is not so difficult. The non-ulcerating tumor when manifesting symptoms of general tuberculosis may be extremely difficult of recognition. It can involve as does the gumma either the inferior turbinate or the septum. In color it may resemble that presented by the gumma or it may have a decidedly grayish appearance. Its size is variable and while solitary it can be at times, as is the gumma, multiple. Additional difficulty in diagnosis is due to the fact that up to recently lupus has been regarded as a separate entity from tuberculosis.

The nasal mucous membrane is, as has been shown by numerous investigators, largely immune to the invasion of bacteria. On that account all the chances are in favor of the swelling not being tubercular. Blood examination will serve to exclude syphilis, and a careful physical examination be apt to reveal some lesion in the chest. A recovery of the tubercular bacillus is extremely difficult and a microscopic examination, however, may be required to completely establish a diagnosis.

The case just reported presents several interesting features. First: All other stigmata of syphilis were lacking. While this is not an infrequent occurrence it is, on account of the situation of the lesion, worthy of comment. Second: The complete relief from all trouble with the nose following the first course of treatment. Third: The relief experienced by the surgical measures instituted. It is a well-recognized observation that any surgical operation in a syphilitic nose is apt to be followed by dire consequences. Repeatedly has this been experienced in operations for correction of deflected septum. The only conclusion that can be drawn is that the infection in this case was only of a low degree of severity. The blood reaction showed only a one plus Wassermann. It is interesting to note, however, that the *particeps criminis* showed a four plus Wassermann.

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## UNUSUAL FORMS OF SYPHILIS OF THE NERVOUS SYSTEM WITH PARTICULAR REFERENCE TO THEIR DIAGNOSIS

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THE physician who confines his activities exclusively to one branch of medicine is likely to believe that certain types of disease, certain cases as they are popularly called, occur more frequently than is generally thought, and that they have greater importance than the rank and file of the profession concede to them. It is readily seen how such belief is engendered. It must, however, be admitted that the specialist is not in a position to give the matter proper valuation. It is after all the "average" practitioner who is in position to do this, providing he does not overlook such diseases, or fail completely to recognize them.

Syphilis of the nervous system, particularly that part of the nervous system situated within the cranial cavity, occurs much oftener than is suspected.

I am convinced that our attention has not been sufficiently called to the various forms in which such infection displays itself, i.e., that the clinical manifestations of cerebral syphilis have not been adequately depicted. I base this statement upon my experience in the Neurological Institute where, during the past few years, opportunity has been given me to study a large number of cases, nearly all of which had been under treatment before coming under my care. Recognition of these cases of syphilis of the brain has been furthered largely by the aid obtained from the laboratory which gives us corroborative evidence of syphilis when the existence of the disease is suspected, at least when it is suspected with sufficient keenness to prompt us to examine the blood and cerebro-spinal fluid. Moreover, the wider dissemination of the fact that individuals may become infected with syphilis without evidence of primary manifestations, namely, a chancre; and that the organism of syphilis often invades the nervous system immediately after infection without giving rise to considerable symptoms for a long time, have all

contributed to give security to the position that we maintain that syphilis of the nervous system is of much more frequent occurrence than is generally conceded. My first thesis is, then, that there are many cases of syphilis of the brain whose real nature is not suspected, especially during the period when it is still susceptible to successful treatment. We must purge ourselves of the belief that syphilis of the nervous system and especially syphilis of the brain displays itself in what is called a pathognomonic or typical way. Such has been the traditional teaching. In medicine one is hampered by tradition. We must forget its maxims and axioms in regard to the diagnostic signs of brain syphilis. If we are going to be guided at all by "rule of thumb," the only safe one to follow is to suspect the existence of syphilis in practically every functional and organic disease of the brain whose origin is not convincingly attributable.

I present herewith a brief summary of a series of cases studied during the past year to corroborate these statements.

#### CASE I.—GENERALIZED SYPHILIS: MENINGEAL SYPHILIS

One of the most unusual cases of syphilis of the brain that I have ever encountered had no symptoms or signs that suggested the diagnosis, and lacking the information furnished by the laboratory, it could not have been diagnosticated. The patient, a lady, 45 years old, unmarried, fell ill six weeks before I saw her, with symptoms of what were considered to be "ptomain poisoning," i.e., vomiting, purging, prostration, and stupor. The symptoms displayed themselves in attacks which lasted about 24 hours each. She had three distinct attacks, 5 or 6 days apart. She had been in ordinary good health until her forty-second year, when she had what was called a nervous breakdown which seemed to follow "neuritis" in the left upper extremity. She went to Atlantic City for the change, but after three weeks there she felt depressed, complained of pain around the heart and in the eyes, and she manifested much fear and self-concern. She then went to the mountains, stayed a few weeks and seemed to recover. For an indefinite time previous to the beginning of the symptoms attributed to "ptomain poisoning" she complained of fatigue, and was inclined to be apathetic, but she had never been energetic. A few days after the last attacks before mentioned she got rigid while seated on the commode, and passed into a

semiconscious state. She was first seen by one of my associates, May 25th, 1916, who found an emaciated, frail, little woman, lying in bed, apparently quite indifferent to her predicament, whose only complaint expressed in a weak, feeble, bored voice, was that she was run down and weak, and wanted to be let alone. She manifested no interest in herself or in her surroundings, often evacuated her bowels in bed, and took food and drink only when urged.

Physical examination was practically negative throughout. The next day she passed into a deeper stupor, and was aroused only with great difficulty. She was completely incontinent, swallowed apparently with difficulty and did not reply intelligently to questions. Physical examination was still quite negative. The following day she answered questions slowly and feebly, and made some effort at cooperation during the examination. She put out her tongue, held out the hand, but with the air and manner of one indescribably bored by it all. Her general appearance and reactions were those of a person in dense mental obscurity. The impression that one got was that the condition was either a toxic, exhaustion psychosis or a mild degree of wet brain. There was no history of alcoholism but the fact that there seemed to be considerable tenderness of the nerves and muscles when subjected to pressure gave plausibility to the latter suggestion. There was no stiffness of the neck, however, and no disorientation, spurious reminiscence, mistakes of identity, which are so characteristic of mild, chronic, meningeal edema due to alcohol. There was no noteworthy structural alteration of the blood, and the excretions of the body susceptible to examination were not abnormal. Examination of the viscera revealed nothing to account for her symptoms. Her temperature was slightly subnormal, systolic blood pressure 95, and the pulse rapid and feeble. One week later it was noted that she was unquestionably improved. The most striking symptom still was physical and mental prostration. On the following day she had a relapse and became very stuporous. I saw her then for the first time. Her appearance was that of a frail, emaciated individual *in articulo mortis*. She paid no heed to commands or request, she seemed quite unconscious. The breath was foul, of a penetrating, sweetish odor. Physical examination revealed marked exaggeration of all the tendon jerks; double ankle clonus, exhaustible patellar clonus; exalted knee, ankle, and triceps jerks; and the Babinski big toe phenomenon was elicitable on both sides.

Blood was taken for a Wassermann examination and a lumbar puncture was done. The patient was then given immediately 400 c.c. of a 3% solution sodium carbonate injected into the left median basilic vein. Further alkaline solution was thrown into the rectum by means of the Murphy drip. She began to improve within an hour after the injection.

The report from the laboratory was as follows:

Serum Wassermann,	+
CSF                   “	+
Globulin,	+
Fehling's,	+
Cells per cubic mm.	9

The following day it was noted that she was more easily aroused, took her food without being forced, displayed a little interest in her surroundings and answered some questions. Physical examination elicited the same condition as on the previous day, save that it was *all* milder. The tendon jerks were less exaggerated and marked, the Babinski sign was not so exquisite. On June 6th, 7th, 8th, and 9th, she received 0.2 gm. arsenobenzol intravenously. On June 7th she could be aroused, she obeyed commands, and answered questions laconically. She recognized her family physician and called him by name, and told him that she felt weak. The tendon jerks at this time were exaggerated, she had a left inexhaustible ankle clonus, the right was exhaustible, and there was a typical Babinski sign on both sides. The abdominal reflex could not be obtained. Examination of the blood serum and cerebrospinal fluid showed a similar state to that of the week before. On June 12th, 14th, 16th and 19th, she was given 0.3 gm. salvarsan intravenously. On June 17th a decided change took place in her condition. She said she felt well. She could not tell when she came to the hospital, but thought she had been there three weeks. She added that this was a judgment on her part rather than a recollection because her sister told her she had been ill nine weeks. She did not recall anything of the onset of her illness, nor how she had been treated. On June 22nd, it was noted that her mental condition was steadily improving. She was fully oriented, recalled having been the occupant of another room some time during her stay in the hospital, the different doctors that had seen her, etc. She displayed, however, a certain querulousness and irritability. She



had a grudge against the doctors; one makes game of her, another is discourteous, another lacks interest, and so on. When it was suggested that this was inconsistent with the care that had been given her, she said she must be crazy. On June 26th, the Wassermann reaction of the serum and cerebrospinal fluid were negative. She was then given another dose of salvarsan and put on general tonic treatment. It was noted that her appearance and conduct were quite changed. She walked with little evidence of weakness, her greeting was affable, her answers responsive, her conversation courteous. She thought she was taken ill some time in March, she did not remember distinctly, but recalled that the last time she went to the table there was shad for dinner, and it tasted very good. She gave a coherent account of her early days in New York, of her family's activities, and of her own life, up until the beginning of June. At the end of the visit I said to her, "This has been the most satisfactory interview I have had with you," to which she replied, "I have seen you but once before." I had seen her every day and oftener for three weeks. Her physical examination at this time revealed no abnormalities. On July 10th, her Wassermann reactions were still negative, and she was given another injection of salvarsan. She seemed to be mentally quite normal. Her speech, conduct, mental reaction, were quite the same according to her family and others who knew her as they were when she was well. She conversed intelligently, played solitaire, was cheerful and companionable. She did not read the papers because all her life long she had read only the headlines, and she knew as much of the news as those who read the whole article. The mental inactivity which she displayed was her usual condition. She could interest herself doing nothing and always had. She entered into conversation with alacrity, discussed current topics, planned to go to the mountains, took an interest in the infirmities and welfare of the patients that she encountered in the exercise and occupation departments of the hospital, and in a general way comported herself like a well person. She was discharged from the hospital June 18th, 1916, and given a mixture of mercury, iodine, and iodide of potassium. On August 15th, she seemed to be in excellent health and had gained 35 pounds. The Wassermann tests of the serum and cerebrospinal fluid were normal. October first, she reported that she was in excellent health.

It is not essential that the diagnosis of the tissues affected by the

syphilitic process be made in order that the disease may be successfully combated. The treatment is the same for syphilis of the meninges, the parenchyma and the bone. It is essential, however, to make such estimation if we would safely foretell the outcome of the disease. To do this one must take into consideration all the facts, those furnished by the history, the examination of the patient, and the laboratory.

In the case just cited, we were probably dealing with two conditions, a generalized syphilosis with predilection of the virus for the meninges, and a profound disorder of the nitrogen metabolism. The dissolution phenomena which the patient displayed and which were so promptly combated by the intravenous administration of carbonate of soda are scarcely to be interpreted on any other grounds. On the other hand, none of the symptoms was really characteristic of meningeal, vascular, or parenchymatous syphilis. The clinical picture was that of an overwhelming toxic state, nor did the laboratory report throw any light on the subject other than to show that the infection conditioning the disorder was syphilitic. Many writers on syphilis warn against giving too much importance to information obtained from examination of the blood serum and the cerebrospinal fluid. While not attempting to detract from the importance of the clinical manifestations of syphilis of the nervous system, I am convinced from experience similar to this that the laboratory examination is often of paramount importance.

#### CASE II.—SYPHILITIC EPILEPSY SYMPTOMATIC OF PACHYMEINGITIS

I have already said that it is not always possible to define the exact pathological process within the cranial cavity, nor can it be too often repeated that it is not necessary to do so in order that the disease may be treated successfully. The following case, an example probably of pachymeningitis with possible involvement of the temporosphenoidal bone, may be quoted as an illustration. It is also a convincing contribution to the claim that the nervous system is often affected very early in the course of the syphilitic infection.

An unmarried man of 32, contracted syphilis in August, 1915, he had the customary local lesion and evidences of infection. He went to a physician who gave him an injection of salvarsan intravenously, but did not make a Wassermann test. He understood from the physician that the injection of salvarsan was all that was necessary to be cured. A few months later, however, he did not feel well and

he went to another physician who made a Wassermann test and gave him salvarsan and mercury treatments, two of the former and three of the latter, the last treatment being shortly before the onset of the attack which brought him to the hospital. He relates that he went to the theater and while sitting there a numbness gradually developed in the feet and legs. He thought he had been sitting too long, and got up and went downstairs, thinking the air would do him good. When he got into the open his right arm and leg began to twitch and jerk, he was about to ask a man to help him when he lost consciousness. When he came to, he found himself in the office of the theater, and an ambulance doctor there, who suggested that he should go to the hospital, as he had had a fit, bit his tongue, and soiled his clothes. He went home instead. He had a severe headache, but the next day he went to work, and continued to do so until the recurrence of the epileptic attacks became so frequent that he was obliged to give it up. He entered the hospital on May 29th, 1916, his complaint being of epileptic attacks, which occurred with varying frequency and severity, sometimes as many as three or four in a day. After the severe attacks he was semi-delirious and incoherent for a time, and lately he had noticed that he did not talk right. His words got mixed up. In addition to these attacks of epilepsy he complained of headache, and of pain in the back. Physical examination, save for slight irregularity of the pupils, was quite negative. The day succeeding his entrance into the hospital he had two mild attacks, in neither of which was he convulsed. He seemed to get dazed, could not speak for about 10 minutes, and afterward complained of intense headache.

The laboratory reports, the Wasserman tests were:

Serum Wassermann,	—
CSF                   “	—
Globulin Excess,	—
Fehling's,	

In view of the fact that the serology was negative throughout, and that there were no somatic evidences of syphilis, it was decided to put him on iodide of potassium, 20 grains, 3 times a day, and to increase the dose by a similar amount each day.

On June 12th, it was noted that the headache continued with great violence, and the past two days he complained of nausea and occa-

sionally vomited. The headache was not affected by change of position. It was no less severe when he lay down than when he sat up. The pain was located in the frontal region above the left eye, it radiated back across the temple to the left ear. He never had pain on the right side of the head. The pain was steady, boring, grinding. The patient kept the left eye closed or nearly closed although he said he had never seen double. When, however, it was not closed, he felt dizzy and insecure. The headache, dizziness, and occasional vomiting continued unabated, and on June 13th, it was decided to give him salvarsan. He received 0.6 gm. intravenously on that day, and 0.3 on June 16th. On June 17th he awakened entirely free of headache, and from that time until his discharge from the hospital, on July 12th, he continued to be free from headache or any symptoms of epilepsy. He received 0.6 gm. salvarsan every 8th day up to August 14th, when he was last seen. In addition he took steadily a mixture of mercury, iodine, and iodide of potassium. He has remained at work from that time until this, quite free of symptoms.

This case is to be interpreted as one of pachymeningitis, the lesion being most intense over the motor cortex, and the epileptic attacks symptomatic of such irritation. The pain of which the patient complained bitterly reminded one of the pain which accompanies periosteal or bone disease, and it is quite possible that such lesion may have existed in this case. The fact, that the symptoms were not relieved until after he received salvarsan, is of interest in view of the fact that the specific reactions of the serum and cerebrospinal fluid were absent. This is an experience that I have had several times. It will be made the subject of another study.

#### CASE III.—DISSEMINATED CEREBROSPINAL SYPHILIS

The more one sees of syphilis of the nervous system, the more fully convinced he becomes that practically nothing is known of the factors that cause involvement of this part or that, and the more keenly we realize that the disorder may be an affection of one part of the nervous system at one time, and of another part at another time. I can cite no better illustration of this than the case of a married lady, 40 years old, mother of 7 healthy children, who is still under treatment. She became infected during her first pregnancy, when she was 21 years old. The infection which was placental was recognized as soon as the cutaneous and mucous membrane manifestations ap-

peared, and she was subjected to the generally approved treatment. From the time of the cessation of this treatment; namely, 2 years after infection, up to her 31st year, she was in fairly good health, but had occasion to consult a physician frequently, principally for what was termed "muscular pains," sharp, lancinating in character, associated with feeling of stiffness, and which were always considered to be rheumatic as they yielded to the administration of the salicylates. During these years she gradually put on flesh until she weighed 190 pounds. Nine years ago, that is, when she was 31 years old, she was seized with severe pain over the right orbit, which was not relieved by the salicylates, indeed its intensity increased from day to day, and after about a week she developed vertigo. This continued for another week or more when she felt nauseated, vomited, and finally had a queer sensation in the left side of the face and body. When these symptoms developed the pain began to mitigate. The doctor who saw her at this time said, she related that she had had a "stroke." There was no inability to use the extremities, however, though her husband recalls that the left side of the face seemed to be slightly drawn for several weeks following it. She took mercury and iodide of potassium during this attack, but as neither the physician nor herself sensed its gravity, the medication was dropped as soon as the symptoms disappeared. One year later she began to complain of double vision and she was put upon so-called "mixed treatment" again until the diplopia disappeared. She then had eight years of comparatively good health, during which time she bore four children. In November, 1915, she began to complain of indefinite pain in the head and spine and of malaise. Soon she was seized with symptoms referable to the digestive tract; viz., vomiting, distress in the abdomen and diarrhea. This continued for 3 or 4 days, and was succeeded by a sensation of numbness in the lower extremities, especially in the thighs and loins, girdle sensation about the pelvis and the lower torso, shooting pains in the left arm and up and down the spine. After this had continued for about 6 weeks or more, she noted an increasing difficulty in standing and in walking, and difficulty in starting the urinary stream. These symptoms continued to progress until when she was first seen April 10th, 1916. She was unable to walk without assistance, her legs giving way beneath her whenever she attempted to do so. She still complained of pain in the left arm and leg, which was shooting in character and oc-

curring in paroxysms, of cramping and jerking of the muscles of the left leg, and of difficulty in initiating the urinary stream. Examination showed an obese woman of flabby musculature, with ataxic, uncertain, hesitating gait, who felt obliged to use a cane in standing or in attempting to walk. The left side of the body was weaker than the right, and the weakness was particularly of the left upper extremity, in which there was typical paresis of the ulnar distribution. She was unable to approximate the little, ring, and middle fingers to the thumb. All the tendon jerks were somewhat exaggerated, but they could scarcely be called pathological. The plantar reflex on the right side was flexor in type and there was a suggestion of a Babinski big toe phenomenon on the left. The superficial reflexes were all elicitable, save the abdominal and epigastric, which were absent. The finger jerk known as the Hoffman phenomenon could be elicited. There was no disturbance of sensibility, either the superficial or deep, and there was no astereognosis. The pupils were irregular in outline, and both responded very sluggishly to light. The discs were normal, and there was no disorder of the muscles of the eye.

The vascular system seemed to be normal as far as it was susceptible to examination, the blood pressure 140, vessels not thickened nor resistant to the touch. The laboratory examination showed:

Serum Wassermann,	—
CSF	“
Globulin,	+
Number cells per cubic mm.,	1
Fehling's,	+

She was put under vigorous antisyphilitic medication, including salvarsan and inunctions of mercury. There was no change in her condition until ten days later, without warning, early in the morning she found she could not speak. She knew what she wanted to say, but she could not express it, and she knew what was said to her. She knew the names of everything that was shown to her, but she could not say them; she knew what was put in her hands, but she could not pronounce the names. At the same time she complained of vertigo and felt nauseated. These symptoms all disappeared within 26 hours, and her condition was the same as before they occurred, save that the urine showed albumin and hyaline casts. On

May 8th she returned for examination and was given 0.2 mgm. salvarsan intraspinously. The cerebrospinal fluid at this time was practically the same as at the last examination. The mercurial administration was continued. On July 14th the laboratory examination, the tests being made by titration, showed:

Serum Wassermann,	80%
CSF           “	80%
Globulin,	—
Cells,	6
Fehling's,	+

She was given another intraspinous injection of 0.2 mgm. salvarsan and kept on mercury inunctions alternating with a mixture of mercury, iodine and iodide of potassium.

She now began to show decided improvement. She walked more securely, without the aid of a stick. She had better control over the movements of the left hand, and she felt much stronger. The spasticity showed no improvement. Indeed it tended to increase. When she was seen on October 3d, 1915, there was well defined Babinski of the left big toe and a suspicion of the Bakinski phenomenon on the right side. There was distinct ankle clonus on the left side and a suspicion of ankle clonus on the right. She was now given 0.6 m. salvarsan intravenously.

This case must be looked upon as a type of syphilis of the nervous system in which the meninges, the blood vessels and the parenchyma are each involved, one displaying the burden of the involvement at one time, another at another; the vascular manifestations predominating until finally the parenchyma becomes most conspicuously affected. The case also illustrates some of the difficulties encountered in thwarting the activity of the virus after it has once involved the nervous system. Between May 6th and October 4th she received 5 intraspinous injections of salvarsan, 3 intravenous, and almost constant treatment by mercury, and mercury combined with the iodides; and neither the progress of the disease nor the evidences of the virus in the blood was particularly altered. It shows also that the laboratory tests cannot be relied upon to guide us in determining whether or not the patient should be subjected to vigorous anti-syphilitic treatment.

## CASE IV.—SYPHILITIC NEURASTHENIA

Many individuals with active syphilis of the central nervous system are looked upon as neurasthenic or hypochondriacal. They are told that they imagine or exaggerate their symptoms, and what they need to do is to forget them, to get more into the open air, to have a change, or similar sapient saws. Early in the present year I saw an intelligent printer, 40 years old, who gave the following history:

He had a chancre 15 years ago which was followed by the customary manifestations of infection. He was treated with mercury by intunctions and by mouth for 2 years. He was then pronounced cured. When he was 34 years old, considering himself in excellent health, he married. He was depressed to find that he was partially impotent. He remained quite well until 3 years ago, when after having contested a fat-man's race, he began to have disagreeable sensations in different parts of the body, but more particularly in the back of the head and neck, as though the neck were going to be stiff; numbness of the left hand and of the lips on the left side; dryness of the throat; disorder of digestion, particularly "heart-burn" and some eructations; general diminution of vigor; and self-concern and absent mindedness. The physical examination showed, aside from psoriasis, no abnormality. Mental examination was equally negative.

The laboratory report was:

Serum Wassermann,	+
CSF                    "	+
Globulin,	+
Lymphocytes,	78
Fehling's,	+

He received the following treatment:

DATE	INTRASPINOUS	INTRAVENOUS	INTRAMUSCULAR
1-6-16	0.3 Salv.	Salvarsan	Hg. Salicylate Gr. I to II every 5th day
1-12-16		0.6	
1-27-16	0.3		
2-9-16	0.4		
2-10-16		Venarsen	
2-17-16		"	
2-28-16		0.6	
3-10-16		0.9	
3-27-16	0.3		



At the end of this time the laboratory report was:

Serum Wassermann,	+
CSF           “	+
Globulin,	+
Lymphocytes,	9
Fehling's,	+

On October 15th, 1916, he reported that he had had treatments as follows: April 7th, an intravenous injection of neosalvarsan, April 11th, an intraspinal, and on April 18th, May 1st, and May 11th, intravenous injections of arsenobenzol. He felt quite well and was conducting his business satisfactorily. The serum Wassermann was positive, and the cerebrospinal fluid showed positive Wassermann, weakly positive globulin, and 107 cells.

This is the type of case that often eventuates in general paresis. From consideration of the symptoms alone, or in conjunction with the results of physical examination, one could not make a diagnosis of syphilis of the nervous system. The results of the examination of the serum and cerebrospinal fluid are so striking that there can not be the slightest doubt of the nature of this patient's ailment or of the gravity of it.

#### CASE V.—MILD VASCULAR MANIFESTATIONS OF CEREBRAL SYPHILIS

It is astonishing how many cases of profound cerebrospinal syphilis there are in which the virus is active, without particular symptoms, or symptoms so slight that the affected individual looks upon them as manifestations of some trifling bodily disturbance. Some of these cases are among the most rebellious to treatment that we encounter.

As an illustration of a typical case, a married man, by occupation a mechanic, became infected with syphilis when he was twenty years old. The early manifestations of the infection were displayed in the skin, mucous membranes and glands. He had very little treatment then, though he knew he had syphilis. His wife had borne no children, she had been pregnant once and miscarried. He considered himself a strong, robust, well man, and sought the advice of a physician, because he had a boil on the forearm; and as he had heard of the peril of syphilis and knowing he had had it, he thought it may have come from that. The physician whom he con-

sulted happened to be under treatment for tabes by me, and sent him to the Neurological Institute. Questioning elicited the fact that he had indefinite, queer sensations in the head at times as if he were going to have headache, and occasionally slight manifestations of dizziness. He recalled that a year before he experienced faint, dizzy sensations occasionally, but he gave no heed to them.

The physical examination was quite negative, save that it showed him to have pupils that were sluggish to light. They were not quite circular and the right had no response whatsoever to the light, while the left was nearly immobile.

The laboratory report was:

Serum Wassermann,	+
CSF                   “	+
Globulin,	+
Lymphocytes per c.m.	56
Fehling's,	+

He was given treatment as follows: January 15th 0.4 gms. arsenobenzol, January 22nd 0.6 gms. arsenobenzol, January 29th 0.6 gms. arsenobenzol.

Laboratory report, January 29th:

Serum Wassermann,	+
CSF                   “	+
Globulin,	+
Lymphocytes per c.m.	56
Fehling's,	+

He was then given treatment as follows: Arsenobenzol 0.6 gm. February 20th, 27th, March 5th, 12th, 19th, 26th, April 2nd, 1916.

The Wassermann reaction on April 2nd, was still positive in both serum and cerebrospinal fluid.

#### CASE VI.—MENINGEAL SYPHILIS

In many instances the diagnosis must be made from consideration of the patient's history and the laboratory findings. In other words, physical examination does not reveal any abnormality, or if such abnormality exists, it is so trifling that it is readily overlooked. The following case is an excellent illustration of the truth of these remarks:

A salesman, 29 years of age, contracted syphilis when he was 18. There were no disturbing manifestations of the infection, and he received only local treatment. He married when he was 22, and his wife became pregnant but miscarried. Since then she has been sterile.

On May 15th, 1916, having been previously in good health, he felt weak and insecure on arising in the morning. He complained of pain over the left eye, sensation that his face was twitching, queer feeling in the right leg, and a feeling as if he were "going crazy." In addition to this he had an indefinite disorder of speech. While he was talking he would lose the thread of his remarks entirely and not know what he was saying. It was as if he lost consciousness a few seconds. He went into a hospital in Philadelphia where a Wassermann test was made of his blood. It was reported negative, so he says, but nevertheless they gave him an injection of neosalvarsan, after which he felt better. He then went into the country and remained there quite free from symptoms for nearly two months. On July 12th, 1916, while in bathing, he became short of breath, and got quite in a panic. He was assisted from the water and by the time he got home the symptoms attending the first attack had recurred.

He came to the Neurological Institute on August 18th, 1916, complaining of pain all over the head, but particularly over the left eye. He maintained that the vision of the left eye was impaired, and when the pain was very severe, he could not see at all with this eye. The headache was continuous, but subject to exacerbation. Sometimes it was worse in the morning, sometimes in the evening. Excitement and haste made it worse. In addition he complained of a choking sensation in the throat, of heaviness in the chest, and of a queer numblike sensation in the right lower extremity below the knee.

Physical examination revealed: (1) Absence of the right plantar reflex. (2) Tactile anesthesia of the right lower extremity, reaching upward nearly to the knee, and then gradually shading off into normality. (3) Diminished knee jerks on both sides, the right being weaker than the left. (4) Exaggerated abdominal, epigastric and cremasteric jerks. There was no tremor, no disorder of speech, and the ocular mechanism was entirely normal.

The examination of the blood and cerebrospinal fluid showed on August 19th, 1916:

Serum Wassermann,	+
CSF           “	+
Globulin,	+
Lymphocytes,	2460
Polymorph.,	240

He was given 0.6 gm. salvarsan intravenously, August 19th, August 24th, and August 31st.

On Sept. 8th, he returned to say that he had been quite free from pain and other symptoms until Sept. 6th, when he began to have darting pain in the left side of the head. It would last 2 or 3 minutes and then go away. The queer sensation in the right leg below the knee persisted but was not so marked as formerly. The laboratory report on this day was as follows:

Serum Wassermann,	+
CSF           “	+ —
Lymphocytes,	108

He was then given 3 doses of salvarsan at intervals of a week, and the blood and cerebrospinal fluid subjected again to examination.

At first sight it seemed that this patient had a rightsided sensory hemiplegia, but on weighing all the evidence furnished by the patient's story, by examination of him, and by the laboratory, the diagnosis of meningeal syphilis, the focus of the inflammatory process being in the left hemisphere over the posterior central convolution, was made with some confidence.

This is a type of patient that we have to bear with for our sins. As soon as his symptoms were relieved he could not be persuaded to continue treatment, no matter how terrifying the picture of his future without treatment was made nor how attractive that of permanent restoration to health.

#### CASE VII.—VASCULAR AND PARENCHYMATOUS CEREBRAL SYPHILIS

The most intractable cases of the nervous syphilis to treat are those that are now generally spoken of as parenchymatous. It is practically universally conceded that general paresis for instance is not susceptible to benefit from treatment. There are many reports of cases which have been benefited by treatment, but the truth is that up to date the disease is beyond the reach of medicine. Many

cases of vascular syphilis are susceptible to treatment, some are not. I have had during the past 7 years since the advent of salvarsan, cases of vascular syphilis that have been under treatment almost steadily, and the manifestations of the disease have been held in check, but the existence of the disease is still evident. No better illustration of such experience can be cited than the case of a young salesman, 32 years old, who contracted syphilis when he was 26 years old, and who had the customary evidences of infection. He was given mercury internally, and later, that is, within the first 18 months, he received 80 injections of mercury. There was no indication of involvement of his nervous system until August, 1913, that is 6 years after infection; he became quite emotional while praying for his dead father, he having attributed his father's death to worry over the nature of his illness. Soon after he left the synagogue, he was seized with a queer sensation in the left side of his face, as if it had gone to sleep, this gradually extended throughout the entire left side of the body. He didn't become hemiplegic. He was able to walk home, but he felt weak and very much agitated. Two days later he began to complain of headache and of vertigo, and these symptoms continued despite the treatment of neosalvarsan, of which he got 3 injections within 6 weeks following this date. He came to the hospital on October 22, 1913, and the only visible sign of syphilis of the nervous system which he presented was the Argyll-Robertson pupil. They were irregular in outline, the right being larger than the left, the left being entirely immobile to light, and the right having a very slight reaction. There was no evidence of motor hemiplegia, but there was a slight distinct diminution of tactile sensibility over the entire left side of the body and particularly of the head and face.

The laboratory examination at that time revealed as follows:

Serum Wassermann,	—
CSF                   “	+
Globulin,	—
Cells,	17
Fehling's,	+

From that time until the present date he has had 29 injections of salvarsan, four weeks' treatment at Hot Springs, Ark., and innumerable injections of mercury and inunctions and despite that, his condition today is practically the same as when he first came under

observation. The headache is not so severe, the dizziness occurs less frequently and is of less intensity, but he is unable to work because of nervousness and mental unrest. It is very difficult for him to define his symptoms, he can not control his brain is the way he terms it. He is well nourished, sufficiently strong to work, and his intellect is just as acute as it ever was. His Wassermann reactions remain positive throughout.

Serum Wassermann,	+
CSF                   “	+
Globulin,	—
Cells,	30
Fehling's,	

He has none of the hallmarks of general paresis, and it is practically impossible to give any clinical designation to his infirmity. To call it neurasthenia is only to obscure the matter unless the word syphilitic is prefixed.

#### CASE VIII.—THE CEREBELLAR SYNDROME DUE TO SYPHILIS

Occasionally we encounter patients whose symptoms do not suggest syphilis in the least and yet when a positive Wassermann reaction is obtained in the blood serum, a diagnosis of syphilis would explain the symptoms better than any other. Such was the case of a young boy, seen only a few days ago. Although he denied syphilis he admitted that a month before the symptoms for which he sought relief began, there had been a small sore with raised edges on the frenum which healed in a week or two and to which he paid no heed. The symptoms which had been in existence about eleven months displayed themselves as, first, unsteadiness in walking, of gradual onset and slow progression, second, by burning sensation over the entire head and intermittent severe pain in the back of the head, third, indistinctness of vision, and fourth, occasional vomiting.

On examination of him there was found:

1. Bilateral, lateral nystagmus. This consists of fine, rapid, rhythmic oscillations which were succeeded by slower, coarser and less rhythmical movements, more pronounced on looking toward the left.

2. Facial asymmetry on voluntary movement. The left side of

the face was less vigorous on voluntary motion than the right.

3. A mild degree of dysmetria in the upper extremities. There was invariably an overreaching in the finger-nose test on both sides.

4. Disorder of station and gait. When he closed the eyes there was a decided tendency to fall toward the left. When he walked the feet were wide apart, the stride was insecure and he tended to pitch toward the left.

5. Inability to pronate and supinate the left hand as rapidly as the right. Although this did not amount to a definite adiadococinesia, it was an approximation to it.

6. The tendon jerks of the lower extremities were lively and the abdominal and epigastric reflexes could not be elicited.

Examination of the special senses showed them to be practically negative. With the laryngoscope it could be readily seen that the left laryngeal muscles did not contract as much nor as readily as the right, especially in going from low to high notes. When he takes a deep breath the right vocal cord abducts quickly, the left sluggishly and only about one-half as much as the right.

In brief, the physical signs and the subjective symptoms are those of cerebellar irritation. Were it not for a strongly positive Wassermann reaction of the blood serum on two successive occasions and from different laboratories, it would be scarcely legitimate to contend that we were dealing with an example of syphilis of the brain. But as tumor, abscess and trophic process can be readily ruled out, the only plausible diagnosis is syphilis or disseminated sclerosis. In the presence of the Wassermann reaction we must look upon the pathological process as a vascular, inflammatory, syphilitic, displaying itself in minute foci through the cerebellar hemisphere and possibly also the oblongata. This patient improved steadily under treatment by mercury. On Nov. 10, 1916, one month after he was first seen, he was so much improved that he went to work.

These cases will suffice to show that it is impossible to lay down any rules by the use of which the diagnosis of cerebral syphilis can be made safely. The belief can no longer be held that the pain produced by cerebral syphilis has certain specificity; that certain forms of ocular palsies are pathognomonic; that multiplicity of symptoms is highly suggestive of syphilis of the brain. One makes the diagnosis of cerebral syphilis with more certainty when the patient displays clinical manifestations which have long been recognized

as dependent upon cerebral syphilis, but it is desirable that the diagnosis be made in cases in which no such symptoms exist. In every instance where symptoms are not reasonably attributed the possibility of their dependency upon syphilitic lesion must be kept in mind and investigations instituted which will corroborate or disprove this.

It is regrettable that investigation of the cause of disease is sometimes construed to be a reflexion upon the chastity of the individual investigated. Our experience has been that so many individuals have had syphilis who were not transgressors of the canons of conduct laid down by Church or State, that we feel the necessity of urging that the possibility of syphilis as the cause of nervous disease should be entertained in every instance, it matters not who the unfortunate individual is. It is now generally recognized that the possession of syphilis is not at variance with what is popularly known as virtue, and, therefore, inquiry may be made concerning its possible existence without giving offence or making an enemy. Making verbal inquiry is of little value anyway. A man who has had syphilis in early life and has been assured by the best authority before he married that he was cured is likely to find it consistent with honesty to deny that he has had the disease. The very great number of wives and children who have become infected by such individuals can not possibly have any knowledge of the disease.

Nervous disorder occurring in an individual who admits previous syphilitic infection and who has a positive Wassermann reaction of the serum, is probably due to syphilis, but it need not necessarily be. In other words, the possibility of the simultaneous existence of syphilis, of disease of tissues, such as the brain or spinal cord due to other causes and especially to other infections and to trauma should not be forgotten. The best illustration of this that I can cite is that of a gentleman of 30 years, who in endeavoring to learn the cause of his wife's sterility, found that her serum and his showed a positive Wassermann reaction. Neither of them had any knowledge of the existence of syphilis nor had they had experience to which it could have been attributed. He was under treatment for two years, during which time he received fifteen injections of salvarsan, each averaging about 0.5 grams and 30 injections of salicylate of mercury, each of from one to three grains. At the end of that time, namely in October, 1915, his Wassermann reaction was still strongly plus.



He consulted me a year later complaining of pain in different parts of the body, particularly in the shoulder blades, back of the head, small of the back, and in the legs, a dull aching pain that prevails from one part to another and is more or less constant. When he awakened in the morning he felt stiff all over and particularly the joints of the hands and feet. Aside from that he did not complain, save that he lacked ambition and energy. Physical examination was quite negative save that the joints of the fingers were somewhat tender to pressure. His case impressed me as one of streptococcus infection, and an x-ray examination of his teeth revealed an abscess on one of the roots. When this was overcome and the patient given appropriate treatment he promptly got well. Contending as I do for the necessity of giving full valuation to syphilis as a cause of nervous disease, I realize that there are other causes. This brings us back to the position that we must always take; namely, that the clinician is the final arbiter.

## THE SPIROCHETAL CONTENT OF THE SPINAL FLUID OF TABES, GENERAL PARESIS, AND CEREBRO- SPINAL SYPHILIS

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THE question of the spirochetal content of syphilitic spinal fluid is a subject which has received but little investigation. Uhlenhuth and Mulzer, in 1913, in determining the infectiousness of syphilitic blood and body fluids, reported negative results following the inoculation of rabbits with the spinal fluid of seven recently syphilitic individuals and four cases of tabes and general paresis. A later observation by the same authors records one positive inoculation in the rabbit testis from a case of early cerebrospinal syphilis. The spinal fluid from this case showed only a moderate pleocytosis and no spirochetes were demonstrable in the fluid before injection. In this case a typical spirochetal orchitis occurred in the rabbit three months following the inoculation. Hoffmann, according to the same authors, was able in a single case to produce experimental syphilis in the monkey with spinal fluid injected from a patient with an early papular eruption. In the same year Nichols and Hough, in attempting to establish a neurotropic strain of spirochetes, were successful in inoculating a rabbit from a case of acute cerebrospinal syphilis by injecting the spinal fluid into the rabbit testis. From this case they were able to isolate and cultivate the organism.

Steiner succeeded in producing three positive takes from the spinal fluid of 20 cases of early syphilis. In all three cases there was apparently no objective change in the spinal fluid. In nineteen cases of tabes, paresis, and cerebrospinal lues reported by the same author, negative results were recorded.

Volk, however, was able to produce a positive result in a single case from the cerebrospinal fluid of a delirious parietic. In this case the positive take was noticed four months after inoculation. Four

other inoculations from similar sources reported by the same author, were negative.

In two cases of early syphilis in which the fluid was entirely negative, Arzt and Kerl were able to produce positive inoculation results in both. The same authors, together with Mattauschek, succeeded in producing positive results in two of four cases of paresis and two out of three of tabes. Marinesco and Minea produced an experimental chancre from the spinal fluid of a case of congenital paresis, the lesion appearing in the rabbit testis five months after inoculation.

During the past year Frühwald and Zaloziecki have reported a large series of cases in which they employed the spinal fluid from primary, secondary, and tertiary syphilis. Of 23 experiments, they reported positive takes in one case of lues I and II, one case of late secondary syphilis, one case of early syphilitic meningitis, and one case of tabes. Reasoner, in June of this year, reported a successful inoculation into the rabbit of the spinal fluid from a patient who died of cerebral syphilis. He was able to successfully cultivate the organism from this case and to establish that the strain possessed unusual characteristics.

As far as the literature at hand discloses, spirochetes have been successfully demonstrated in the spinal fluid in isolated instances only. Dohi and Tanake in 1905 demonstrated spirochetes in a single case of early syphilis out of a great many investigations. Sezari and Paillard found spirochetes in the dark field from a case of left-sided hemiplegia. Gaucher and Merle found them in the ventricular fluid of a similar case of hemiplegia. Levaditi, Marie and Bankowski found them in the centrifugated ventricular fluid of a case of paresis, and Graves found them in the fluid of a case of spinal lues ten years after infection. For the most part, however, the search for the organisms in the fluid itself has been unsuccessful even in those cases in which positive inoculation has demonstrated their presence.

The question as to the spirochetal content of the spinal fluid is a matter of very great importance not only for the bearing that their presence may have upon the pathology of the disease, but also from another standpoint. The spinal puncture has today become a routine measure in all well regulated hospitals and is performed, or should be at least, at some time during every syphilitic's lifetime. I have been impressed with the relative carelessness with which clinicians

handle spinal fluid. It not infrequently happens in withdrawing the stilette or in collecting the fluid that more or less is spilled over the operator's or attendant's fingers, and in the laboratory the possibility of the fluid being a source of infection is customarily entirely disregarded. If spirochetes are present in spinal fluid the same great care should be used in examination as is employed in the examination of other syphilitic products and secretions.

At the University Hospital clinic specimens of spinal fluid are withdrawn from every patient having syphilis upon entrance into the hospital as a routine diagnostic measure. Many unsuspected cerebrospinal involvements have been uncovered by this routine procedure.

During the past year I have inoculated the spinal fluid from eight cases of acute cerebrospinal syphilis, general paresis, and tabes dorsalis into the rabbit testis. The results which are detailed herein have fully fortified my belief based upon the original observations of Uhlenhuth and Mulzer, Nichols and Hough, and others, that the spinal fluid contains spirochetes and that as such it is an infectious fluid. Injections of the cerebrospinal fluid from two cases of acute cerebrospinal syphilis resulted in positive takes in both. Injections of the spinal fluid from three cases of general paresis resulted in positive findings in two. Injections of the spinal fluid from three cases of tabes dorsalis resulted in a positive result in one and negative in two.

Following is a brief outline of the cases with the results in detail of the experiments:

*Case 1.*—Lues I and II. Neuro-recursive. Severe headache following salvarsan injections. Wassermann on the blood +++. Lumbar puncture: cells 259, albumin ++, Nonne-Apelt positive 1 to 1. Fluid under very high pressure. Wassermann on the spinal fluid +++. Edema of optic discs.

Examination of the spinal fluid for spirochetes with the dark field, negative after prolonged examination.

Two c.c. of the spinal fluid was injected into each testis of a rabbit December 8, 1915. December 20, testes slightly enlarged; *Spirocheta pallida* in moderate numbers found in both. January 5, 1916, (two weeks later), testes larger; no nodes, however. *Spirocheta pallida* found in large numbers. February 4, moderate numbers of organisms. No nodes. April 6, condition as before. From this time on the number of organisms decreased until after a few weeks they were no longer demonstrable.

*Case 2.*—Cerebrospinal syphilis. This case was one in which the lumbar puncture revealed a rather marked involvement without the patient's having known

that he had spinal involvement. Syphilis 15 years ago. Patient entered the hospital for gumma of the toe, gumma of the testis and gumma of the epididymis. The neurological examination was negative. The spinal puncture showed a cell count of 155; Albumin positive; Nonne-Apelt positive 1 to 10. Wassermann +++ on blood and spinal fluid. On the basis of this finding, intraspinal treatment was instituted with very prompt change for the better in the objective findings in the fluid.

Prolonged examination of the spinal fluid failed to reveal spirochetes in the dark field.

December 20, 1915, 2 c.c. injected into the rabbit testes. January 5, testes slightly enlarged. No nodes palpable. Moderate numbers of *spirocheta pallida* from the aspirated testicular juice. A second examination February 9 failed to reveal spirochetes, and none were subsequently found.

*Case 3.*—General paresis. Syphilis eight years ago. Present condition, marked failure of memory, occasional apoplectiform attacks, inequality of pupils, parietic facies, marked speech defect, euphoria. Blood Wassermann +++. Spinal puncture; 56 cells, albumin and Nonne-Apelt positive.

Prolonged examination of the spinal fluid under the dark field failed to reveal spirochetes. Wassermann reaction on the spinal fluid +++.

Two c.c. of the spinal fluid injected into the rabbit testes January 12, 1916. Five days later *spirocheta pallida* found in moderate numbers. These for the most part were short and thicker than ordinarily found and did not show any great degree of motility. The testes were slightly enlarged but there were no nodes. February 7 a few spirochetes were demonstrable. Testes same as before. Subsequent examinations were entirely negative.

*Case 4.*—General paresis. Syphilis 20 years previously, contracted at the age of 13. Was brought to the hospital for evidence of mental deterioration. A neurological examination showed inequality of the pupils and sluggishness to light in both, increased reflexes, no sensory disturbances. Patient very euphoric. Blood Wassermann +++. Lumbar puncture: 48 cells, albumin positive, Nonne-Apelt positive 1 to 5. Wassermann on the spinal fluid +++. Colloidal gold typical parietic curve. Careful examination of the spinal fluid under the dark field failed to reveal spirochetes.

January 22, 2 c.c. of the spinal fluid injected into rabbit testes. Repeated examination following this inoculation for a period of five months failed to reveal any change in the organ, and no spirochetes.

*Case 5.*—General paresis. Syphilis 15 years previously. Examination showed inequality of pupils, both Argyll-Robertson. Marked increase in the superficial reflexes. Marked speech defect. Fine tremor about the muscles of the face. Wassermann on the blood +++. Lumbar puncture; 25 cells, albumin positive, Nonne-Apelt positive 1 to 5. Wassermann +++. Colloidal gold typical parietic curve. Examination of the spinal fluid in the dark field failed to reveal spirochetes after prolonged search.

January 31, 1916, 1½ c.c. injected into the rabbit testes. At no time following this were any spirochetes demonstrable. On the 15th of April, however, 2½

months following the inoculation, the rabbit developed a small hard node in the right testis, marked coryza and alopecia of the head and neck. No organisms, however, were demonstrable from aspirated juice from the node.

*Case 6.*—*Tabes dorsalis.* Syphilis fourteen years previously. Inequality of the pupils and both Argyll-Robertson. Knee and Achilles jerks both absent. Slight Romberg. Wassermann on the blood +++. Lumbar puncture: 3 cells, albumin positive, Nonne-Apelt positive 1 to 1. Wassermann reaction positive.

Careful examination of the spinal fluid in the dark field failed to reveal spirochetes.

February 5, 1916, 2 c.c. injected into the rabbit testes. Subsequent repeated examination failed to reveal any change in the testes, and no spirochetes were found.

*Case 7.*—*Tabes dorsalis.* History of syphilis indefinite. Sharp shooting pains in both legs since eight years. Girdle sensation. Argyll-Robertson pupil. Lost knee and Achilles jerks. Marked Romberg. Wassermann on the blood positive. Lumbar puncture: 50 cells, albumin positive; Nonne-Apelt positive 1 to 10. Wassermann positive. Examination of the spinal fluid revealed no spirochetes after prolonged search.

February 16, 1916, 2 c.c. of spinal fluid inoculated into rabbit testes. Four days later aspirated testicular juice showed a few irregular and small spirochetel forms. From this date on until four months after inoculation, no more organisms could be demonstrated.

*Case 8.*—*Tabes dorsalis.* Syphilis 25 years ago. Sharp shooting pains for the past 15 years. Numbness around the waist. Pupils pinpoint, and Argyll-Robertson. Marked tremor of the tongue and mouth. Loss of knee and Achilles jerks. Marked Romberg. Spinal fluid 26 cells, albumin ++, Nonne-Apelt positive 1 to 5. Wassermann on blood and spinal fluid +++++.

Examination of the spinal fluid failed to reveal spirochetes after prolonged search in the dark field.

February 8, 1916, inoculation of 3 c.c. of spinal fluid into rabbit testes. Subsequent examination failed to reveal any change in the testes themselves and no spirochetes were found at any time up to four months following the inoculation.

These results contain some interesting data. In the first place, in not a single case was a permanent experimental syphilis in the sense of a definite testicular nodule, elicited. In all the cases in which the spirochetes were positively found, these remained in the testis and then gradually disappeared. The interpretation of this finding is somewhat difficult. It may very well be that the organisms in the spinal fluid were in too small a quantity or too attenuated in virulence to produce permanent lesions in the rabbit. The second possibility which suggests itself is that notwithstanding the failure to find the organisms in the fluid before the injections, that these were

present and that they persisted in the rabbit testis as survivals. In this case their disappearance might be explained upon their transplantation to a new soil. Inasmuch, however, as the rabbit testis has shown itself an ideal soil for spirochetal culture, the latter explanation would hardly seem to suffice.

It would seem that the absence of a distinct nodule in the rabbit testis must not be regarded as proof of a non-take. Swelling of the organ without definite nodule formation occurred in three cases, and in all these cases, organisms were found for a variable length of time. The possibility that the spirochete may exist in the spinal fluid as a resting stage has been suggested, although Zinsser, Hopkins and Gilbert, as well as Uhlenhuth and Mulzer, doubt the existence of any ultramicroscopic forms.

Whether or not such resting stages, ultramicroscopic or not, exist, the presence of spirochetes in the spinal fluid must be accepted in the light of our present knowledge that they exist in the nerve tissue itself which is bathed by the fluid.

So far as I have been able to ascertain, there are no recorded cases of accidental syphilitic infection from contact with cerebrospinal fluid. Such an accident, however remote, must be regarded as possible in the light of this and previous investigation. In the University Hospital clinic at the present time we exercise the same care in handling spinal fluid as in the handling of any of the more infectious syphilitic secreta.

A further point of some interest lies in the fact that those cases were positive in which there was a high pleocytosis. This suggests at least that the organism may be in some way connected with the lymphocytes. That this is not invariably the case, however, is illustrated by the case before mentioned of Uhlenhuth and Mulzer, in which the lymphocytosis was not great. I am inclined to believe that the spinal fluid in any case of cerebrospinal syphilis of whatever form, contains spirochetes at certain times during the course of the disease. The negative inoculation results mean nothing. The quantity of fluid used may have been too small, the organisms in an attenuated condition, or physical conditions in the one medium so different from those in the other that they did not flourish. The high percentage of positives, 62½%, is a far more significant finding.

## CONCLUSIONS

From this study may be concluded:

1. The spinal fluid from cases of early syphilis, of tabes and of paresis, contains spirochetes, as demonstrated by transplantation into the rabbit testis.

2. The spirochetes may be present in moderate, or even large numbers in the rabbit testis without producing the classic gumma or chancre of the testis. In some cases slight enlargement of the testis itself may be noticed. In still others spirochetes were demonstrated in which no increase in size of the testis was noted. In no case in this series were spirochetes demonstrable in the fluid itself before inoculation.

3. The spinal fluid, at least in cases in which the nervous system is involved, must be regarded as infectious, and as such should be handled with the same care as other syphilitic secretions.

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## SYPHILIS OF THE STOMACH\*

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**A**LTHOUGH numerous cases are being diagnosed clinically as syphilis of the stomach, as judged from the reports in the literature, it is a rather peculiar fact that practically all pathologists still consider such a condition as more or less of a curiosity. Certainly a review of the literature upon syphilis of the stomach reveals comparatively few syphilitic lesions of that organ in which the diagnosis has been made by histological examination, while the number of cases diagnosed clinically alone, as syphilis of the stomach, runs up into the hundreds.

To those at all familiar with the literature on gastric syphilis, the name of Chiari will be well known. He,<sup>1</sup> in 1891, published a classical contribution upon this subject. In this review Chiari accepts as authoritative cases only eight of those hitherto reported, basing his rejection of other reported cases upon the lack of sufficient pathological proof. In addition to these cases, however, Chiari reports two new cases of his own, and also reports the results of a series of autopsies done upon 243 syphilitics, in which these two cases were the only syphilitic lesions of the stomach which were found. Later, in 1893, Bittner<sup>2</sup> described three more cases, and Stolper,<sup>3</sup> in 1896, one additional case, the latter being the only one found among a series of 86 autopsies done upon known syphilitics. Since that time Flexner,<sup>4</sup> in 1898, has added still another case of syphilitic ulcer of the stomach which was demonstrated at autopsy. In this article he describes the lesions in detail and also gives a critical survey of the literature to date. Hayem and Lion,<sup>5</sup> in 1913, report four more such cases, demonstrated by histological examinations, and Farey, quoted by Cronin,<sup>6</sup> reports a case showing gummata in the wall of the stomach. Quite recently, in 1915, the author<sup>7</sup> has had the privilege, also, of studying a syphilitic ulcer of the stomach microscopically, the ulcer having been removed under the mistaken diagnosis of cancer of

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the stomach. Holland<sup>8</sup> has also reported a case of supposed cancer of the stomach, which on coming to operation was considered inoperable. A gland, however, being removed at the time, showed lesions resembling those of tuberculosis. Since this case recovered entirely when placed upon antisyphilitic treatment, it may well be considered syphilitic ulcer or gumma of the stomach, although it was only partially diagnosed histologically. Finally, in 1916, Symmers<sup>9</sup> analyzing autopsies done on syphilitics in Bellevue Hospital, New York, reports only one case of gastric syphilis among 314 cases of syphilis coming to autopsy. This, moreover, was the only case occurring in a series of 4880 autopsies upon all classes of patients.

When one turns, however, to the literature dealing with syphilis of the stomach which has been diagnosed clinically, he finds innumerable reported cases. Einhorn,<sup>10</sup> in an excellent article published in 1900, gives a review of the cases reported up to that time, and reports three new cases in detail. In another article,<sup>11</sup> published in 1915, the same author again surveys the literature on this subject and reports several more cases of his own, concluding that the disease is by no means so rare as is generally supposed. Meyer,<sup>12</sup> in 1912, reported two clinical cases of gastric syphilis which were studied in detail. Morgan<sup>13</sup> reports eight cases; Clark,<sup>14</sup> eleven cases; Smithies,<sup>15</sup> 26 cases; and Downes and LeWald,<sup>16</sup> eight cases, the latter authors describing the roentgenologic as well as the clinical findings in this condition. In addition to the cases mentioned, numerous other reported cases are to be found in the literature, which, for the sake of brevity, will be omitted here.

Regarding the pathological lesions caused by the involvement of the stomach wall with the *spirocheta pallida*, three distinct lesions are supposed to be caused; these consisting of gummata, ulcerations, and scar tissue. Gummata of the stomach are usually found in the muscular coats or upon the peritoneal aspect of the stomach wall and are not so common, apparently, as are the ulcerative lesions of the gastric mucosa, which peculiarity is perhaps due, as has been suggested, to the fact that a gumma situated adjacent to the gastric mucosa is apt to become digested by the secretions and, breaking down, to form an ulceration. A gumma remaining intact in the stomach wall, however, resembles the usual gumma found elsewhere, and as a matter of fact, such gummata are usually found in other parts of the body at the same time.

The ulceration of the gastric mucosa caused by syphilis is, according to pathologists, fairly characteristic of the disease. Pathologists differ, however, as to the method in which these ulcerations are formed, some claiming that they are the results of the gastric digestion of previous gummata, while others claim that they are more commonly due to an obliterating arteritis of syphilitic nature, which condition is usually found in more or less marked degree in all of these lesions. Most authorities are agreed, however, upon the fact that the syphilitic ulceration involves chiefly the submucosa of the stomach; that an arteritis and periarteritis are present, which are usually most marked in the submucous layer, and that there is a tendency for the formation of granulation tissue around the borders of the ulcer. The base of such ulcers is usually formed by the muscularis mucosa. The edges of the ulcer are thickened due to proliferative changes in the submucous layer. Patches of degenerated and necrotic mucosa may be noted, due probably to the obliterative endarteritis. These necrotic patches are more apt to be noted around the edges of the ulcer. The size of the ulceration may vary from millimeters to several centimeters in diameter. It may be located anywhere in the stomach from the cardia to the pylorus. The majority of the reported cases have, however, involved either the greater or the lesser curvature. Syphilitic ulcers of the stomach are not infrequently multiple. Often other organs than the stomach are involved simultaneously, the liver being the organ most frequently involved. Perforations<sup>†</sup> or fistulæ\* may be formed by the ulcerations. Numerous dense adhesions between the affected stomach and the adjacent organs are occasionally present.

After a syphilitic ulcer or gumma has healed, cicatricial tissue takes the place of the active lesion and constrictions may occur of a serious enough nature to cause obstruction to pyloric or cardiac openings.

Since such lesions as those described are by no means commonly found in syphilitic individuals coming to autopsy, and are not even found in those districts where syphilis is especially common,<sup>†</sup> how are we to explain this marked discrepancy between the numerous

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\*Case No. 2.

†Out of 1080 autopsies done in this clinic during the past few years, about three hundred of whom were syphilitic clinically, not a single syphilitic ulceration of the stomach was found; nor were any evidences of previous ulcerations such as scar-tissue formation demonstrated in any of these syphilitics.

examples of clinical syphilis of the stomach and the few instances of pathologically demonstrated syphilis which have been reported?

The explanation is, apparently, simple, and is based upon the fact that the large majority of individuals suffering from tertiary lues, sooner or later, if the disease is not treated, complain of some form of gastric distress. This observation is based upon the study of all syphilitic individuals who have been admitted to the medical clinics of the John Sealy Hospital during the past few years. A study of the records of those cases of syphilis who complained of gastric distress will show that in practically every case some other organ than the stomach was primarily involved in the process, and that the gastric distress was, more often than not, the result of reflex disturbances from this other organ. As an example of such reflex gastric disorders caused by tertiary syphilis in other organs than the stomach, the very common condition, in this clinic, of syphilitic involvement of the liver is an excellent illustration. During the early stages of such involvement the first complaint of the patient is practically always referred by him to the stomach, and not infrequently the stomach gets the brunt of the blame both on the part of the patient and physician. This is more particularly true, of course, during the early stages of the hepatic involvement, before any appreciable enlargement of the liver has taken place, during which stage tenderness over the liver is practically the only objective sign which is commonly noted. Moreover, during such involvement of the liver, while the stomach is most frequently suspected of being at fault, certain changes in the nature of the gastric secretion are, in our experience, frequently noted. These changes consist usually of a more or less marked diminution in the free hydrochloric acid secretion. As an example of such change in gastric secretion, we shall refer briefly to eleven cases of syphilis of the liver, observed within the past three years in this clinic, in which the gastric secretion has been thoroughly studied. Of these, eight were diagnosed clinically alone, and three cases came to autopsy also. Of the eleven cases, three showed a complete absence of free hydrochloric acid on every occasion,\* five showed a marked diminution of free hydrochloric acid and only three showed what might be called a normal secretion. In no case of this series was a hyperacidity noted. Frequently, along with an anacidity or hypoaecidity a marked excess of mucus is noted in these

\*As a rule, in this clinic, three tests are made on three different days.

individuals. Certainly in such cases as these, the majority of whom improve promptly upon antisyphilitic treatment, a diagnosis of syphilis of the stomach would not be unreasonable did we not know that organic lesions of the stomach due to syphilis were more or less of a curiosity in the autopsy room.

Syphilis of the pancreas is another excellent example of the ease with which the stomach may be accused when neighboring organs are diseased. Moreover, it is well known generally that the early symptoms of syphilitic involvement of the central nervous system are particularly apt to affect the stomach among the first of all the organs of the body. It is scarcely necessary, finally, to mention the fact that syphilitic involvement of the heart or kidneys is apt to be noted first as some form of gastric derangement.

Bearing the foregoing facts in mind, we have examined the records of the John Sealy Hospital, covering some 1200 individuals, who were considered clinically as syphilitics, the diagnosis being based upon positive Wassermann reactions in each case, and, in a large percentage upon the presence of clinical symptoms as well. In all of these cases, however, the Wassermann reaction has been positive. Of these 1200 individuals, only two cases have occurred in which a definite diagnosis of syphilis of the stomach has been made; of this 1200, however, 97, or about eight per cent have complained of some more or less serious form of gastric distress.†

After a study of three cases diagnosed clinically as syphilis of the stomach, which have come under our observation, and a survey of the literature covering the cases hitherto reported, in which fairly satisfactory evidence of actual organic syphilitic ulceration of the stomach was present, I believe that a fairly typical clinical picture may be drawn for these cases. Also, I believe that this picture may be best described by appropriating the textbook descriptions of cancer of the stomach. It has been stated that syphilitic ulcer of the stomach may be differentiated from cancer by the absence of marked emaciation in the former disease. With this statement, however, I cannot agree since, of the three cases which I shall report, all showed evidence of considerable loss of weight. In only one case, however, was any considerable degree of anemia present, and in this case the anemia was relatively slight considering the severity of the symptoms.

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†We have included among these 97 cases only those showing signs of real gastric distress, such as vomiting, severe pain, or tenderness, etc.

Since the three cases which I shall report are fairly typical, clinically, of syphilitic ulceration of the stomach, I shall limit the description of the symptoms of the ulcerative state of the disease to those cases.

The symptoms of cicatricial syphilitic involvement of the stomach have been well described by Einhorn in the two articles previously mentioned; such symptoms will naturally vary with the location of the scar tissue formation. If at the pylorus, the picture will be that of pyloric stenosis, granting that the lesions be extensive enough to produce obstruction. Hour-glass stomach formation has been reported from syphilitic involvement. Symptoms caused by gummata in the wall of the stomach, and not involving the mucosa are certainly not so severe nor so typical as are those of syphilitic ulcer. In fact, no definite symptoms referable to the stomach may be present at all in such conditions, particularly if the gumma be small and single. On the other hand epigastric pain and tenderness associated with tumor formation may be noted<sup>17</sup> in this condition. Gummata of the wall of the stomach may be said, however, to possess no definite symptom complex.

The cases which I wish to report are as follows; all probably being syphilitic ulcerations of the gastric mucosa:

*Case 1.*—A negro laborer, aged 50, complained of pain in the stomach after eating. The family history was negative, except that the wife had one late miscarriage. The personal history was negative for any trouble bearing on the present illness. There had been no stomach trouble before the onset of the present illness. The patient denied lues but admitted gonorrhea.

The present illness began three months before admission, with a sharp pain in the upper epigastrium, radiating to the right side, appearing from one-half to one hour after meals, being fairly constant in appearance, but varying in intensity. It was never before severe enough to become a definite colic. Acids appeared to increase the pain. The patient thought he had lost some weight, the amount of which was not known, but probably about 20 pounds.

Physical examination revealed nothing abnormal except tenderness on pressure over the epigastrium, especially just to the right of the midline. Examination of the blood showed a slight anemia (4,300,000 reds; hemoglobin 65) but nothing else of interest. The Noguchi test for syphilis was positive.

Stomach analysis after an Ewald meal showed an absence of free hydrochloric acid, a total acidity of 25, occult blood and lactic acid and Oppler-Boas bacilli. Microscopic examination of the empty stomach contents, removed by means of a Jutte duodenal tube, revealed nothing abnormal. The tube passed through the pylorus with some little difficulty (1 hour) but as soon as it had become engaged in the pylorus, an interesting change in the microscopic appearance of the con-

tents was noted. Numerous pus cells, with a mixture of red blood cells, were noted, along with a large number of cylindrical and globular gastric epithelial cells, giving a very different picture under the microscope from that obtained in the first stomach contents removed. The duodenal contents were normal cytologically and chemically.

The patient was placed in bed, and on specific treatment (mercury and potassium iodid) for two weeks. At the end of this time, there was no demonstrable improvement in his condition. The pain was as bad as before. He was afraid to eat on account of the discomfort. At this time it was noted that the administration of hydrochloric acid after meals seemed to increase the pain.

In view of the absence of any improvement in the gastric or general condition of the patient after two weeks of antiluetic treatment, it was deemed advisable to perform an exploratory laparotomy on the suspicion of the presence of malignant condition. At operation, a marked annular thickening was made out, encircling the first part of the pyloric-region. There was a general enlargement of the pyloric lymph-nodes. Also, several large mesenteric lymph-nodes were observed. Several of the pyloric nodes were as large as Lima beans. A resection of the pylorus was done. The specimen removed at operation showed an annular, apparently active ulcer, almost completely encircling the first part of the pylorus. The submucosa appeared to be most involved. The edges of the ulcer were undermined and soft, but considerably thickened. The floor was smooth. At one extreme end there appeared to be an attempt at healing. Microscopically, the picture was one of degeneration, chiefly of the submucosa, but affecting also the muscular layers to some extent, with a marked periarteritis of all the arterioles. The mononuclear elements played almost the entire part in the periarteritis. At the point where the attempt at healing was suspected, there was an evident growth of new connective tissue (granulation tissue). The large lymph-nodes showed a simple hyperplasia.

The patient made a good recovery from the operation, received a dose of salvarsan and a thorough mercurial treatment, and was as well as ever when last heard from, about eight months after the operation. The histological specimens were submitted to several competent pathologists and all agreed that the picture was that of syphilitic periarteritis. No spirochetes could be demonstrated in the sections.

*Case 2.*—Negro man, laborer, 43 years of age. Complaint, pain in the stomach. Family history, negative. Past history, negative except for history of chancre 19 years ago. Present illness began in September, two years ago, with acid eructations and epigastric pain coming on from twenty to thirty minutes after eating. The discomfort was so severe at that time as to cause patient to stop work for several months. During the following spring he started again, however, but was forced to stop on account of a severe recurrence of his symptoms, accompanied this time by severe attacks of vomiting. Since then patient has been losing weight steadily and becoming progressively weaker. Is unable to eat any solids at all without vomiting and severe pains.

Physical examination shows a markedly emaciated man but is otherwise nega-

tive except for marked epigastric tenderness and rigidity. Blood examination shows 4,800,000 reds and 79% hemoglobin. Wassermann strongly positive.

Gastric analysis after Ewald meal shows a complete absence of free hydrochloric acid; total acidity 20; lactic acid present; Oppler-Boas bacilli present. Occult blood present. Wolff-Junghans' test, positive.

X-ray examination shows a fistulous opening between the stomach and the small intestine, probably the jejunum, the passage of bismuth being noted readily through this fistula as soon as it is taken into the stomach. Examination of the empty stomach contents reveals large quantities of pus cells well mixed with blood cells; lactic acid; Oppler-Boas bacilli. Tip of duodenal tube passes through the fistulous opening between stomach and small intestine very readily. Duodenal contents normal in appearance, except for the turbidity caused by the pus cells already mentioned.

Stools: Occult blood on numerous occasions.

Diagnosis: Either carcinoma of the stomach or syphilitic ulceration with perforation into small intestine.

This patient was placed upon salvarsan (two doses), followed by mixed treatment, and after one month of this treatment was discharged as cured, being able to eat anything without the slightest discomfort, including *beans* and *cabbage*! Moreover, he had gained 35 pounds within that time. This patient when last seen, about one year later, was a stout well nourished man, able to do any kind of work and still able to eat any form of food desired. He had absolutely no stomach trouble whatever according to his statement.

Case 3.—A white man, aged 48, a machinist by trade. Complaint, vomiting, pain in the stomach. Family history, negative. Past history, alcoholic excesses for years. Chancre 10 years ago. Present illness: ten days ago patient began to suffer from pains in the epigastrium coming on after eating. This was also associated with vomiting. Vomitus had a typical "coffee ground" appearance on one occasion. Had noticed a black tarry-like stool on one occasion. Vomiting has continued up to date, patient having been able to retain very little solid food up to date of admission.

Physical examination, beyond a marked pallor and considerable tenderness and rigidity in the epigastrium, revealed nothing of further note. Blood showed a red count of 4,500,000; hemoglobin 90% and a strongly positive Wassermann.

Gastric contents showed free hydrochloric acid 5% and a total acidity of 43%. No lactic acid nor Oppler-Boas bacilli. Occult blood present.

Stool examination showed tarry stools. Occult blood positive.

Examination of the empty stomach contents showed numerous free pus and red blood cells.

Wolff-Junghans' test, positive.

Diagnosis: Either gastric cancer or syphilitic ulcer of the stomach. Course of disease: Under salvarsan and mercury all unpleasant symptoms rapidly disappeared, patient gaining in strength and now being able to eat practically any kind of food desired by him. Wassermann still positive after treatment, which is being continued. Patient has gained steadily in weight since treatment was commenced.



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## SYPHILIS OF THE STOMACH

### A CLINICAL STUDY OF THIRTY-FIVE INSTANCES OF ORGANIC GASTRIC LESIONS ASSOCIATED WITH POSITIVE WASSERMANN-NOGUCHI REACTIONS

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NEARLY two years ago, I placed on record<sup>1</sup> observations upon twenty-six patients affected with organic gastric lesions, the blood sera from whom exhibited positive Wassermann-Noguchi reactions. The report attracted considerable attention largely on account of the fact that it had previously been presumed that syphilitic lesions in the gastric wall were uncommon. It is a significant fact, however, that in the interval elapsing since the publication of our first report, more instances of gastric lues have been placed on record than are contained in the literature for three decades previously. This recently indicated prevalence of the ailment is largely a result of the more general use of serologic tests in differential diagnosis of intraabdominal complaints.

The present report comprises observations made upon thirty-five dyspeptic individuals whose blood sera were Wassermann-Noguchi positive, and whose clinical examinations disclosed definite gastric pathology.

#### INCIDENCE

Our thirty-five cases occurred in the examination of 8,341 patients affected with all types of dyspepsia. This returns an approximate frequency of one instance out of every 330 gastric cases (.42 per cent). Of this number there were 1760 instances in which the gastric disorder was associated apparently with demonstrable pathology in the stomach or duodenum. Of these, 2 per cent were luetic. The relative incidence of the syphilitic affection is emphasized by noting

that in this group of cases, gastric cancer was found in 17 per cent, gastric ulcer in 18.2 per cent, duodenal ulcer in 41 per cent, achylia or gastritis in 23.4 per cent.

#### PATHOLOGY

The lesion may be congenital or acquired. It is doubtless always part of a general systemic syphilis, but the luetic lesion may be grossly manifested but locally in the stomach. The infrequency of the affection as a part of general syphilis is shown by the statistics of Chiari.<sup>2</sup> From necropsies in 243 pathologically demonstrated cases of lues, of which in 145 cases the disease was hereditary and in 98 cases, it was acquired, he noted that, while *indirect* changes in the stomach wall (circulatory anomalies, interstitial hemorrhages, toughness of the tissues, etc.) are relatively common, *lesions directly attributable* to lues (ulceration, gummas, and scarring) were infrequent.

Careful descriptions of luetic lesions in the stomach have been made by Flexner,<sup>3</sup> Neumann,<sup>4</sup> Chiari,<sup>2</sup> and Weichselbaum,<sup>5</sup> while clinical classifications depending thereon have been advanced by Hemmeter,<sup>6</sup> Einhorn,<sup>7</sup> Kohn,<sup>8</sup> Morgan,<sup>9</sup> Downes and LeWald,<sup>10</sup> McNeil,<sup>11</sup> Brugsch and Schneider,<sup>12</sup> and Eusterman.<sup>13</sup> It would seem, from the nature of the ailment pathologically, that a close histoclinical grouping were possible.

Recent observations of Warthin<sup>14</sup> at the Pathological Laboratory of the University of Michigan promise to throw an interesting and valuable light upon the prevalence of syphilitic lesions in the gastrointestinal tract. Warthin has definitely demonstrated the existence of histopathologic changes in the pancreas similar in every respect to those existing in chronic syphilitic foci in heart muscle, aorta, etc. In many of Warthin's specimens, careful staining by the Levaditi method reveals spirochetes. It is more than likely that similar studies made upon sections of extirpated gastric walls from instances of lues presenting abnormalities of the stomach will disclose lesions very similar to those that Warthin has shown in the pancreas.

These definite pathologic observations should be of great value clinically. They should lead to earlier thought of the possibility of syphilis producing numerous types of gastric disorder, and should frequently indicate proper therapy in cases that have resisted ordinary routine treatment.

Apparently the syphilitic virus first manifests itself as a dense round-cell infiltration of the loose, areolar tissue of the stomach wall. There is frequently an associated endarteritis. When the disease has once become firmly established, it appears to produce four rather characteristic types of lesion: (1) diffuse infiltrations, confined to the areolar tissue, causing thickening and stiffening of the gastric wall ("*Cirrhosis Gastrica*"); (2) local changes in submucosa and mucosa in the form of dense groupings of lymphocytes which may end as typical, miliary gummas; or coalesce, necrose, and slough to form ragged-edged ulcers, not infrequently multiple; (3) single or multiple inflammatory nodules, composed of exuberant connective tissue and lymphocytes; these may involve the entire stomach wall and produce extensive tumors (ulcerating or nonulcerating), stenoses, and malformations in contour; and, (4) subperitoneal and peritoneal invasions, resulting in perigastritis associated with thickening of the wall of the viscus and dense perigastric adhesions. Doubtless by proper manipulation of the Levaditi technic, spirochetes will ultimately be demonstrated in all the types of lesion above described.

As a consequence of these pathologic variations, the clinical manifestations of the malady differ widely. Grossly, they may be summarized as those associated with chronic gastritis, ulceration (with or without stenosis), gastric tumor (with or without obstruction) and perigastritis, often with involvement of adjacent viscera.

#### ETIOLOGY

*Sex.*—In the series forming the basis of this study, there were of the 35 cases, 22 men and 13 women.

*Age.*—The minimum age was 19 years; the maximum, 66. The minimum age for men was 19; for women, 26. The maximum age for men was 60; for women, 66. The accompanying table indicates the age incidence by decades for the sexes:

TABLE SHOWING AGE AND SEX INCIDENCE OF GASTRIC SYPHILIS

Years	Number of Men	Number of Women
0 to 10	0	0
10 to 20	1	0
20 to 30	3	4
30 to 40	5	2
40 to 50	5	3
50 to 60	6	3
60 to 70	2	1
Total	22	13

It was noted that the average for women was 40.8 years and that for men 41.3 years, a sex difference of .5 years.

#### THE LUETIC LESION

It was often difficult to get a history of the primary sore. This is particularly apt to be the case with women. Of the men, genital chancres were recorded in 9, buboes in 4, mouth or lip lesions in 2. In the women genital chancre was reported three times. In two cases there had been mouth sores; in one, buboes. Definite knowledge of venereal disease in the husband was obtained in five instances; in two, the husband's condition was questionable. Of the entire group, there were nine cases in which no history positive for, or suggestive of, lues could be obtained; nor could external evidences of previous lesions be seen. The Wassermann-Noguchi tests were, however, definitely positive.

*Time of Gastric Disturbance After Acquirement of Lues.*—Information in this line is but relatively correct, especially for the women. The average shows that there was but slight variation in the sexes. Two years was the minimum quiescent period for both sexes, while the maximum was, for men, 38 years, and for women, 45 years.

*Stage of the Disease.*—So far as we were able to judge, we had no instance of a congenital affection. In three males and two females, the ailment appeared late in the secondary stage of lues. In the remaining cases (30) the gastric disorder was, etiologically considered, a tertiary manifestation.

*Previous Specific Therapy.*—Of the twenty-one cases who gave definite or suspicious history of chancres or buboes, but eleven had had antiluetic treatment. Of these only five had received a thorough course of mercury and iodid. Four had been given salvarsan for "anemia" within five years of their coming under observation.

#### WASSERMANN-NOGUCHI REACTIONS

These were positive in all our tabulated cases and furnish the basis of our classification. Inasmuch as the nature of the ailment demands diagnosis other than surgical or from sections of tissue removed at laparotomy or necropsy, we fail to see how another basis for classification could be adopted. Certainly, dependence solely on the "therapeutic test" of the effect of antiluetic medicines is not sufficient proof of the disease, for it has been shown that oc-

asionally sarcomas, tuberculous lesions or other inflammatory affections are favorably influenced by salvarsan, mercury, or iodids. If carefully controlled, only rarely is the positive serologic test associated with disease other than syphilis. In grave anemias, malignant cachexia, or alcoholism, dubious Wassermann reactions are occasionally obtained. However, such factors were ruled out in our group of cases.

#### THE GASTRIC MALFUNCTION

*Duration of All Gastric Disturbance.*—Facts of considerable significance are brought out by analyses of this phase. It has been stated frequently that gastric syphilis manifests itself rather abruptly in late life without any previous digestive disorder having been noted. Other observers have suggested that the ailment causes great cellular damage to the stomach wall early in life. Our study indicates that the average duration of dyspepsia was 7.2 years for the group; the minimum duration was six months—a male aged 60; the maximum 25 years—a female aged 52 years. There was practically no difference in the average duration between the sexes.

*Duration of the Presenting Gastric Complaint.*—The average time for the group was 9.7 months; the minimum was four weeks, and the maximum 4.2 years. In women dyspepsia caused the patient to seek relief rather earlier than in men.

*Types of Gastric Histories.*—The wide variations in the pathology of syphilis of the stomach indicate that a great range is possible in the clinical picture presented. In the literature, too much emphasis has been placed upon gastric syphilis at its tumor stage ("surgical syphilis"). It will be recalled that histopathologically, gummatous formation indicates an approach to the terminal damage which the syphilitic virus is capable of producing. It is quite evident that the maximum worth of medical treatment of this affection is possible before gross deformity of the stomach wall and loss of secretory function have occurred.

My cases group themselves quite readily, with regard to the clinical course of the dyspepsia, into three divisions: (1) instances in which a persistent gastric derangement appeared in individuals who had previously experienced no digestive disturbance; (2) instances in which a constant dyspepsia followed years of antecedent indigestion of the intermittent type; (3) instances in which con-



Fig. 1.—Partial pyloric obstruction to luetic pyloric ulcer. Patient, male, age 34.



Fig. 2.—Large, firm, indurated luetic, antral ulcer, with partial obstruction; second ulcer on lesser curvature, indicated by incisura. Patient, male, age 41.



Fig. 3.—Large, penetrating greater curvature ulcer, with perigastritis and extensive adhesions to spleen; stomach wall very thick, tough, and stiff. Patient, male, age 38.



Fig. 4.—Tough, saddle ulcer involving antrum, with partial stenosis; incisura on greater curvature. Patient, female, age 35.







Fig. 5.—Gummatous ulcer, with hourglass. Patient, male, age 41.



Fig. 6.—Multiple, luetic ulcers involving pylorus and antrum; thick, tough, fibrous stomach wall. Patient, male, age 31.





Fig. 7.—Gumma, bleeding type, involving antrum and pylorus, with partial stenosis; palpable epigastric mass before treatment. Patient, male, age 54.



Fig. 8.—Ulcerating gumma, involving antrum, with stenosis. Patient, female, age 27.



Fig. 9.—Large ulcerated gumma, involving pyloric third of stomach; palpable epigastric mass. Patient, male, age 52. Before treatment.



Fig. 10.—Same case as Fig. 9, showing stomach after three intravenous injections of salvarsan and mercury by fumigation and iodide by mouth. Patient symptomatically well.



tinuous gastric disorder arose in persons who had been affected gastrically at some past period, but who had been, for years, free from digestive disturbances. In luetic patients, it is often difficult to ascribe gastric disorders to definite pathologic change in the stomach wall unless the dyspeptic disturbance has preceded evidences of later developing cerebrospinal changes. The roentgen demonstration of gastric deformity is of much service in the doubtful cases. Each clinical type will be summarized briefly.

*Group 1.*—Three of the thirty-five instances of gastric syphilis studied comprise this group. All were men who gave histories of genital primary lesions. In one, the dyspepsia appeared shortly after secondary skin lesions had subsided, in the others it was the only evidence of a tertiary lesion. The affection was characterized by rather abrupt onset of epigastric pain and soreness, constant in character, but varying in intensity; by anorexia, moderate weight loss, constipation, pyrosis, eructations, epigastric tenderness, and, in one instance, a freely movable epigastric nodule, associated with delayed vomiting. Gastric analyses revealed a fairly low formol index, absent Wolff test, and moderate hypersecretion, without hyperacidity. In the case associated with epigastric nodule, fluoroscopic examination disclosed a filling defect of the pylorus and antrum. In the other patients, roentgenoscopy pointed to pyloric ulcers of the chronic, uncomplicated variety.

*Group 2.*—This division was made up of 12 cases (34%). The histories exhibit two rather strikingly different phases of disease: (1) an early dyspepsia, characterized by frequent attacks of discomfort which has the clinical aspect of recurring peptic ulcer, and (2) a subsequent period of continuous indigestion, which frequently presents an aspect different from that exhibited by the first portion of the ailment.

The average duration of all symptoms in the first phase of the disease was 8.3 years. It varied between seventeen months and twenty-three years. The histories indicate a gastric derangement associated with periodic attacks of epigastric distress ("burning," "gnawing," "sore," "ache," or "colic") not uncommonly more pronounced at night or when the stomach was empty, irregular vomiting (hematemesis in two instances), water-brash, good appetite and body nourishment, and abdominal tenderness. In the intervals between attacks, even without treatment, the patients were

generally comfortable. So closely do symptoms and signs simulate those of nonulceric recurrent gastric ulcer, that the clinical differentiation, without the knowledge of specific infection or positive serologic test, is quite impossible. Five patients in this group had taken so-called ulcer "cures" repeatedly, and five of them had submitted to surgical exploration: in three, ulcer of the stomach had been noted, and posterior gastroenterostomy performed.

The average duration of all symptoms in the second portion of this group was 1.3 years. The shortest period of discomfort was seven weeks; the longest, nearly three years. This phase of the ailment was different from that preceding it, in the sense that the patients were *constantly* annoyed by epigastric distress, frequently aggravated at night, and often of sufficient severity to require opiates (50 per cent). During this stage, weight loss was not uncommonly rapid and of marked degree. The average weight loss in three months preceding the time that the patients appeared for examination was 16.2 pounds. There was one case in which weight loss was mentioned as "slight." The least weight loss definitely recorded was 6 pounds, the greatest 47.

Epigastric pain and tenderness were generally most marked in the right upper quadrant. In six instances (50 per cent) there was a palpable epigastric mass. Pain was most commonly relieved by limiting the amount of ingested food, by lavage, and the taking of alkalis. In four instances persistent vomiting developed, with coincident evidences of marked gastric stagnation. Test meals revealed an average total acidity of 34.6, and average free hydrochloric acid, 27. In only two instances was hydrochloric acid absent. The highest free hydrochloric acid noted was 110. Twelve-hour retention was demonstrated in four cases. In eight instances in which the formol index was estimated, it averaged 9.6. In three instances the Wolff test for soluble albumin was positive, but was negative in six. Lactic acid was observed twice. In the case in which hydrochloric acid was absent, organisms simulating those of the Oppler-Boas group were recorded.

Roentgenoscopy returned the diagnosis of chronic peptic ulcer or suspicious ulcer or "tumor" of the stomach in nine instances. In only one case had the question of syphilis been considered. In seven patients exploratory laparotomy was performed. In four instances, smooth, pale, calloused ulcers were noted (in one case three



Fig. 11.—Large ulcerated gumma, involving pyloric fourth of stomach, with partial obstruction.  
Patient, female, age 52.







Fig. 12.—Small, firm, gummatous ulcer, involving pylorus and lesser curvature, with obstruction.  
Patient, male, age 45.





Fig. 13.—Large gummatous ulcerated infiltration of entire stomach wall with extensive tumor formation at the antrum and with stenosis. Patient, male, age 59.



ulcers were noted on the anterior wall and one on the lesser curvature). The stomachs of two patients exhibited a profuse infiltrating scirrhus growth, one with a small nodule on the lesser curvature. In the remaining cases, smooth, hard tumors occupied the pyloric portion of the stomach.

From the above summary of cases making up Group 2, it is seen that the clinical course strongly simulates that of chronic peptic ulcer which later undergoes malignant degeneration—with this exception, however, that while anemia, weight loss, pyloric obstruction, cachexia, and epigastric nodule or ridge may be present, the gastric analysis reveals moderately high total and free hydrochloric acid with no increase above the normal formol index, and with only irregular manifestations of a positive Wolff test. Some stomachs exhibit very rapid emptying. This is not due to vigorous peristalsis, but seemingly, to the stiff, thick, gastric walls permitting food (especially opaque, roentgen meals) to “drop” into the jejunum as does water through a funnel. At laparotomy the diagnosis is often in doubt, but surgeons of experience have learned to leave undisturbed the well-delimited, hard, plaque-like ulcers and the firm nodular tumors which arise from a stomach wall, already thickened by diffuse, infiltrating, exuberant connective tissue. It is in this class of case that information of vital value is received from the serologic test. Its result frequently determines the advisability of surgical interference.

*Group 3.*—Twenty cases composed this division. The early portion of the histories in these instances is not characteristic of any definite clinical type of intragastric disease, associated with any special, gross, anatomic lesion. Previous to the terminal complaint, the early gastric disturbance has made itself manifest in spells often at long or irregular intervals. Not uncommonly, the different attacks exhibit no similarity as to type. In this group, the average duration of the early gastric dyspepsia was 10.2 years. The shortest period of seven months; the longest twenty-eight years. In this first stage the indigestion was variously associated with epigastric discomfort (often styled “vague ache” with tightness and burning), and frequently complicated by irregular, colicky attacks. Cord changes were not observed. The pain was usually situated in the pit of the stomach, or right epigastrium, but rarely had a definite point of localization. Pain relief was commonly obtained by diet, alkalies, vomiting,

the ingestion of food or the administration of an opiate. In but five instances did the epigastric distress bear any definite relation to food intake. This type of gastric malfunction eventually terminated in a stage in which the dyspepsia was constant. There then ensued loss of appetite, constipation or constipation alternating with diarrhea, and weight decline averaging for the group, 19.6 pounds. In six instances there were epigastric ridges or masses, in two cases such were complicated by pyloric obstruction. The test meal revealed an average total acidity of 46.2, and average free hydrochloric acid of 28. There were only three instances in which hydrochloric acid was absent. In eleven instances in which the formol index was estimated, it averaged 9.7. In the same group the Wolff test was positive four times. Roentgen record of an intragastric condition simulating chronic ulcer or tumor was obtained in eleven cases. In the remaining instances, the examination was not made, or its result was questionable. Surgical exploration was performed in ten cases. Laparotomy disclosed chronic ulcer or single and multiple fibrous nodules. In one case the stomach appeared thickened and the mucosa was congested and velvety but was otherwise negative. The gall-bladder was filled with stones.

The above description of cases making up Group 3 demonstrates that although the early part of the history may differ markedly from that composing the first portion of that outlined by Group 2, the terminal stage and the laparotomy findings are strikingly similar to it.

#### LABORATORY DATA FOR THE ENTIRE SERIES

*Blood.*—In seventeen cases in which hemoglobin was estimated, it averaged 78 per cent. The variations were from 20 to 90 plus per cent.

*Stool.*—Of seventeen cases tested for occult blood by the benzdine technic, positive reactions were obtained in four.

*Test Meals.*—Persistent, twelve-hour retention was demonstrated in eight instances (22 plus per cent).

*Gastric Acidity.*—In but five cases was absent hydrochloric acid proved. The average free hydrochloric acid for the group was 29.4 and the maximum 110. The average total acidity was 41.4. The maximum was 114. This was a short term case included in Group 3 in which pyloric stenosis with a palpable epigastric nodule was



Fig. 14.—Gumma involving antrum, pylorus and lesser curvature. Patient, female, age 44.  
Palpable, epigastric tumor.







Fig. 15.—Gumma involving pylorus, antrum and lesser curvature. Patient, male, age 50.  
Palpable, epigastric tumor.





Fig. 16.—Multiple gummiata of stomach with partial pyloric obstruction. Palpable, epigastric nodules. Patient, male, age 56.



observed. Combined hydrochloric acid and acid salts averaged 10.2. The minimum was 0 and the maximum was 36. The presence of lactic acid was determined in the gastric contents from three cases (11 per cent).

Altered blood was proved to be present in nine gastric extracts (28.8 per cent).

The Wolff-Junghans' test was positive in seven cases in the entire group. The formol index, as estimated by the formaldehyd titration method suggested by Sorenson and Schiff, averaged for the group 9.6. The minimum was 6 and the maximum 14. It would seem that this test when interpreted in the light of clinical history and other laboratory data promises to furnish an important point of differentiation between syphilitic and malignant lesions, inasmuch as we have shown that, in a series of eighty-seven gastric cancers and ulcera carcinomatosa, the average formol index is 21.

*Microscopic Examination of Unfiltered Gastric Extract.*—In these, using the colored agar staining method, budding yeasts were demonstrated in eleven cases (43.3 per cent); sarcines in four cases (15.3 per cent) and organisms apparently of the Oppler-Boas type twice (8.8 per cent).

#### INFORMATION DERIVED FROM ROENTGENOSCOPY

Usually neither fluoroscope nor plate methods return pathognomonic signs. The roentgen method may ocularly demonstrate deformities in gastric contour, but in the main such deviations from the normal might readily be observed in benign or malignant peptic ulcer and carcinoma, scirrhus or medullary. Not infrequently, where hour-glass deformity is absent, rapid gastric emptying is seen. Where hour-glass exists there may be lagging of the opaque meal in one loculus with early emptying of the other. Crater ulcers not rarely exhibit local retention flecks. These may be multiple. Such are rather characteristic, inasmuch as nonluetic gastric ulcer is seldom multiple. It has seemed to us that a roentgen sign of some worth were to be deduced from the rather anomalous finding of a gastric tumor or extensive deformity, associated with a fairly high degree of peristalsis and with test meal returns showing normal, or slightly reduced free hydrochloric acid. When a positive Wassermann-Noguchi test is concomitant, the diagnosis is established with reasonable certainty. Not rarely, the roentgen demonstration of extremely small gastric nodules, multiple ulcerations, or tumor formation

proves suggestive enough to lead to the making of serologic tests and the beginning of specific therapy.

#### TREATMENT

The most satisfactory results are obtained by the intravenous injection of salvarsan, followed by a thorough course of mercury (by fumigation, inunction, or hypodermatically and iodids. Not infrequently, the anemia coincident with the disease demands the free use of iron and arsenic. The associated dyspepsia may urgently call for relief by such measures as diet, alkalies, lavage, or, for the pain, opiates. Stenoses that cannot be remedied by appropriate diet call for frequent gastric lavage. Such procedure is often necessary early in therapeutics.

It would seem that one should be cautious about speaking positively regarding the cure of gastric syphilis. Inasmuch as we have shown that the disease may exist for years and manifest itself frequently by periodic digestive disturbances, it behooves us to be careful in telling a too optimistic story of the value of specific treatment. Should the case be one of the type associated with infrequent attacks, it is quite possible that such attacks would have become quiescent even without the administration of medicines. In treating the continuous stages of the ailment, one rarely obtains complete cessation of all symptoms and signs. Extensive destruction of the secretory mechanism of the stomach can rarely be remedied. In our series when reliable data were available, but five patients were wholly freed from dyspepsia for so long as a year. Seven patients were not benefited at all, while twenty-three patients appeared to experience considerable amelioration of their gastric disturbances.

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## SYPHILIS OF THE STOMACH IN ITS ROENTGENOLOGIC ASPECTS

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A STEADILY increasing number of case reports evidences a growing interest in the subject of gastric syphilis. The difficulty of establishing a diagnosis of this condition beyond cavil, as Eusterman<sup>1</sup> suggests, has doubtless deterred the publication of many cases in which the proofs, though reasonably convincing, would not withstand captious criticism. To substantiate the diagnosis one must rely upon the history, the concurrence of syphilitic lesions elsewhere, the Wassermann or Noguchi reaction, the improvement after anti-luetic therapy, and the microscopic examination of gastric tissue. It is quite clear that no one of these is absolutely decisive, unless spirochetes can be demonstrated in the excised gastric tissue by the microscope. Yet a correlation of all the evidence from all sources may maintain a diagnosis as conclusively as many other diagnoses which are freely accepted.

From the material published it would appear that there are three varieties of gastric syphilis: (1) syphilitic gastritis; (2) syphilitic ulcer; (3) syphilitic gummata, hyperplasia, sclerosis, and tumor-formation.

The theory that most syphilitics have gastric syphilis, and that in the eruptive stage they have an eruption in the stomach like that on the skin has been quoted by Myer.<sup>2</sup> However, syphilitics may have gastric symptoms arising only indirectly from their infection, medication may be responsible for digestive disturbance, and the gastric crises of tabetics may be mistaken for gastritis, so that the diagnosis of a simple syphilitic gastritis, without gross tissue-changes, is not indisputable. In any event, the condition is not of immediate interest to the roentgenologist, since the x-ray examination would have chiefly a negative value by its failure to show any organic lesion.

The occurrence of luetic gastric ulcer is well established by case reports. Neumann<sup>3</sup> claims that 20 per cent of the round ulcers occur

in syphilitic persons. Downes and LeWald<sup>4</sup> state that gastric syphilis is characterized histologically by the development of gummata, single or multiple, which originate in the submucosa and go on to infiltration, ulceration, and cicatrization in varying degrees. McNeil<sup>5</sup> records an annular syphilitic ulcer almost completely encircling the pylorus. Brugsch and Schneider,<sup>6</sup> in a clinical analysis of over a hundred patients with tertiary lues who had gastric symptoms, found 13 who had signs of gastric ulcer. Cases of ulcer have also been reported by Fenwick,<sup>7</sup> Tuohy,<sup>8</sup> Portis<sup>9</sup> and Eusterman.<sup>1</sup>

The gummatous, hyperplastic, or infiltrative type of gastric lues is of particular roentgenologic interest, because by the x-ray a gumma or extensive thickening of the gastric wall can usually be demonstrated more easily than an ulcer. Notwithstanding the claim that gastric gummata tend to break down before attaining large dimensions, many exceptions have been noted in which the gummata were of large size. Cronin<sup>10</sup> has collected cases from Cornil and others in which gummatous infiltrations were found ranging in diameter from 2 to 24 centimeters. One of Myer's<sup>2</sup> two cases had a tumor the size of half an orange; the other as large as a hen's egg. Similar cases in which the tumor-mass was of considerable size have been reported by Meyers,<sup>11</sup> Christie,<sup>12</sup> Muhlmann,<sup>13</sup> Holitsch,<sup>14</sup> Mills<sup>15</sup> and Morgan.<sup>16</sup> In these cases instructive observations were made with the roentgen ray.

The symptoms alone of gastric syphilis are insufficient to distinguish it from other organic, or even functional, disorders of the stomach. The pain, which is of diverse degrees, is usually referred to the epigastrium, and varies from case to case in its relation to the taking of food. Vomiting occurs in a high percentage of cases. The infrequency of hematemesis in syphilitic gastric ulcer has been pointed out by Fenwick,<sup>7</sup> but some instances of severe hemorrhage have been reported. The gastric analysis most often shows an achylia, and the suggestiveness of this sign has been emphasized by several observers. However, an achylia is more likely to be attributed to gastric cancer; and if, in addition, a tumor-mass is palpable, the diagnosis of cancer will seem most logical.

Although the roentgen signs of gastric lues, whether of the ulcerative or hyperplastic form, are not of themselves distinctive and pathognomonic, they usually furnish decisive evidence of gastric pathology, and, in correlation with the clinical and laboratory findings,



give indispensable aid in arriving at a diagnosis. In the ulcerative type the cases reported by others, as well as those observed in our series, showed hour-glass contraction as their principal sign. Absence of a niche, accessory pocket, or typical incisura—classic signs of simple gastric ulcer—was notable in most cases, the only exception being that recorded by Portis,<sup>9</sup> in which case both an accessory pocket and incisura were present. A casual study of the cases reported suggests that visceral syphilis is characterized chiefly by infiltration, and that the gastric ulcers seen are abrasions or shallow erosions of the infiltrated gastric wall; hence their multiplicity and their failure to show a niche. In the hyperplastic type, the roentgen signs of a gastric lesion become still more emphatic. The distortion of the gastric outline by filling defects is marked, and this may be associated in various combinations with shrinking of the gastric capacity, stiffening and lessened mobility of the gastric walls, absence of peristalsis, and gaping or obstruction of the pylorus. If the filling defect is associated with a corresponding palpable mass the whole picture is that of a cancer, and the examiner will at first be inclined to make this diagnosis. However, there are two considerations which may save him from this error: First, notwithstanding the extensive distortion of the stomach, no corresponding mass may be felt and the filling defects are evidently due not to the intrusion of a tumor, but to an infiltration and contraction of the gastric walls. Second, the roentgenologist may be impressed by the discrepancy between the extent of gastric involvement and the general condition of the patient, who is often below the cancer-age, is anemic rather than cachectic, gives a longer history than that commonly given by cancer patients, *and, on the whole, is not ill in proportion to the extent of disease shown by the x-ray.* In common with other x-ray workers I have occasionally fancied that there was something in the roentgen appearances of gastric syphilis which helped to distinguish it from cancer, but upon reflection I am convinced that the disproportion between the patient's general condition and the condition of this stomach as revealed by the x-ray is the dominant, perhaps the sole, distinguishing feature, and this, of course, cannot be final and absolute.

Besides cancer and syphilis, there are two other lesions which must be borne in mind; namely, fibromatosis and tuberculosis. Fibromatosis, the "leather-bottle" stomach, which is either benign or

malignant as you prefer to believe, is also characterized by chronicity, and the patients maintain a fairly good physical condition for a long time. The roentgen manifestations of fibromatosis, at least in the cases which I have seen, were not different from those of an infiltrative gastric syphilis. Tuberculosis of the stomach commonly affects the pyloric end of the stomach with the production of multiple ulcers and more or less infiltration. Multiple ulcers have also been observed in the ulcerative form of syphilis. While gastric tuberculosis shows definite roentgen evidence of an organic lesion, the character of the process can only be predicated by the exclusion of other lesions.

Obviously, then, an affirmative diagnosis of gastric syphilis requires the earnest cooperation of the clinician and the laboratory worker. As a purely scientific problem, it is beset with doubt and difficulty; as a practical problem, it can often be solved with reasonable certainty by the exercise of reasonable care, and to this every patient is justly entitled. Thus he can sometimes be spared a needless resection of a supposed cancer, or, if operation be necessary, it can be followed up by effective therapy. Among those cases which should be subjected to extraordinarily careful judgment are the cases of gastric ulcer with an achlorhydria, hour-glass stomachs without a niche, markedly contracted stomachs, the cases showing roentgenologic evidence of a gastric lesion which is not typical of either ulcer or cancer, and the cases in which the x-ray findings resemble those of cancer, although the patient is under cancer-age, and the case as a whole lacks the pronounced characteristics of cancer. In such instances the Wassermann test should not be omitted, and antiluetic therapy should be instituted if the test is positive. This procedure is especially indicated if the gastric lesion is manifestly inoperable. If the lesion is operable, the proof that it is syphilitic should overcome all reasonable doubt, since the patient's right to immediate surgery for a resectable cancer should not be endangered. Thus, on the one hand, the avoidance of a needless operation, and on the other hand, avoiding delay of a needed operation require an abundant exercise of common sense and fair judgment.

From over a score of cases of gastric syphilis, fairly proved, or strongly suspected, which have been under roentgenologic observation in the Mayo Clinic, I have selected the following example:

*Case 141491.*—Woman, aged 30, married, no children, one miscarriage at 7 months. About six years ago, for a period of a year and a half, she was treated

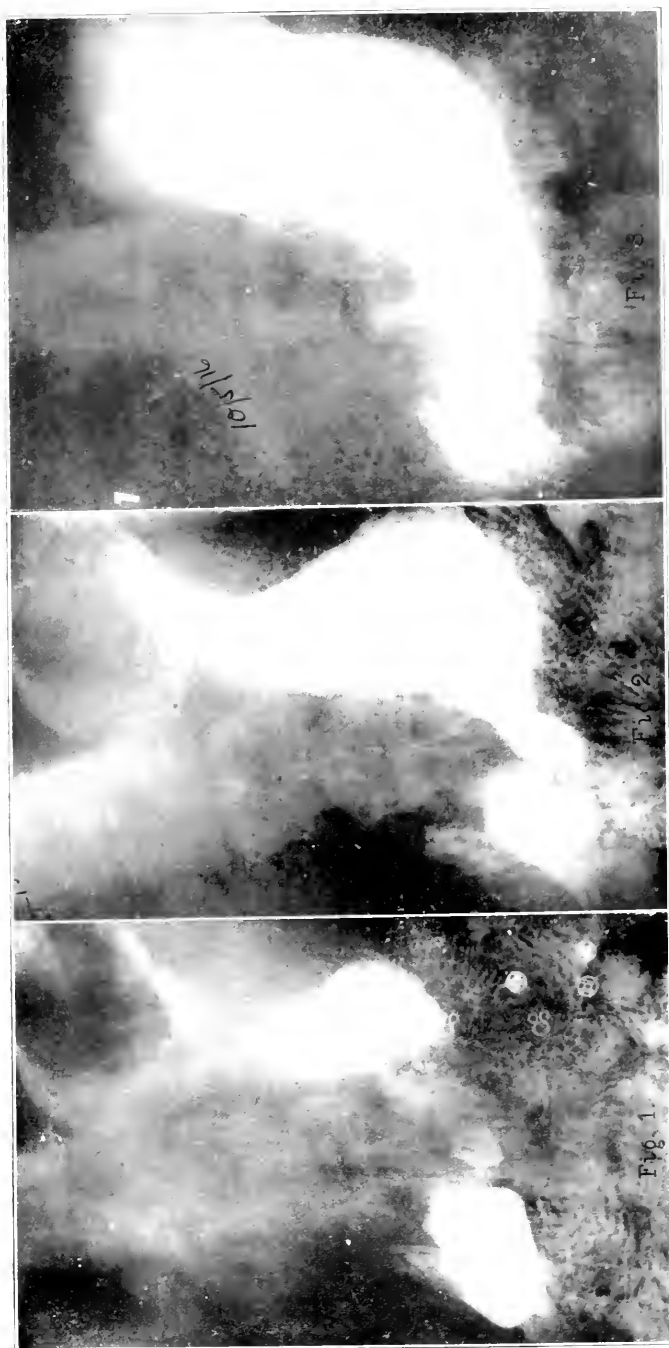


Fig. 1.

Fig. 2.

Fig. 3.





Fig. 4.





Fig. 5.

Fig. 5.





for syphilis. For six or eight months past she has been troubled with bloating, vomiting, and epigastric soreness. The condition was aggravated by ordinary food in ordinary quantities, and for some time she has taken baby-food only. In six months her weight has declined from 135 to 84 pounds. Her general appearance does not indicate malignancy. Urine shows a trace of albumin, otherwise negative. Hemoglobin 80. Gastric analysis: Total acidity, 8, all combined, no food remnants. On three occasions the Wassermann test was strongly positive. First roentgen examination (Oct. 11, 1915): No retention from the six hour meal. Marked filling defect pyloric portion; no corresponding palpable mass. Gastric capacity reduced. Pylorus gaping (Fig. 1.) Diagnosis: Syphilis or cancer of the stomach. (Syphilis was thought of first because a filling defect of this size and in this situation if due to cancer would give rise to a palpable mass and probably to a six-hour retention.)

From all the findings a correlated diagnosis of gastric syphilis was made and the patient was placed on antiluetic treatment, including salvarsan, mercury, and iodids. The results of treatment were strikingly apparent in the subsequent roentgenograms, and the improvement in the roentgenologic appearance of the stomach was accompanied by a corresponding improvement of the patient's general condition.

Fig. 2 is the roentgenogram taken Nov. 27, 1915. The filling defect has diminished markedly. Fig. 3 is the roentgenogram made Oct. 5, 1916, practically a year after the first examination. It shows a normal stomach with normal peristalsis running all the way to the pyloric ring, and normally flexible gastric walls as determined by palpation during the screen examination.

Figs. 4 and 5 are the roentgenograms of two other cases of gastric syphilis.

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## LUES AND THE BABY\*

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THE subject of this paper is one which should be of prime interest to any physician whose professional experiences involve the care of the infant or young child, or in whose responsibilities are included the recognition and treatment of lues in the parenthood of future generations. While this paper primarily concerns lues in the baby, it is clear that this subject also involves the consideration of the parents of the luetic babies before the latter are born.

There are two types of lues in the baby (1) acquired, and (2) congenital or hereditary. The former does not differ from the disease in the adult as there is always an initial lesion (the chief differential diagnostic symptom between acquired and inherited lues), and the course, symptoms and diagnosis are the same as in the adult. It is a rare type of the disease in infancy.

The latter, referred to as congenital or hereditary, is that type of the disease which is inherited from the parents and is the one which concerns this paper particularly. The two terms, congenital and hereditary are synonymous. One, however, is intended to indicate the presence of the disease at birth and the other the evidences showing themselves later. As it is impossible for the disease inherited to be absent at birth the needlessness of the use of the two terms is apparent.

In no disease is the necessity for noting and interpreting objective symptoms more essential. In a previous study of over 350 cases in only 13% of the positive cases was there an admission on the part of the parents of the existence of the disease and in the study the utmost care was exercised in the taking of the histories. It is essential therefore not to be misled by statements of the parents or guardians of the little patients, but to endeavor to secure as thorough histories as are available, as it is possible that some information may be ob-

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tained which may at least suggest the possibility of the existence of the disease. The history should include the age, health, both past and present, of both parents; the number of children, their ages, and condition of their health, both past and present; and the history of miscarriages and still-births with their relation to the pregnancy of the patient.

If all the information from the foregoing examination is fruitless and beyond suspicion, it must be remembered that the most important evidences are to be obtained in the history and examination of the patient. Is he full term or premature? What is his state of development? Has he much hair? Are the fontanels abnormally large? Are the sutures unusually opened? Is there a cold in the head or a noise when breathing? Are there any fissures? Is the spleen palpable and is the liver enlarged? The skin eruptions, scaling palms and soles, bone and eye lesions may be present early or appear later.

While it must be remembered that some of the foregoing symptoms may exist in conditions nonluetic, it must be well borne in mind that if any of them are present lues must be excluded rather than proved. In a large series of cases studied very closely with all possible means available for the proper diagnosis, it has been the experience of the writer to observe cases in which there were present one or several of the symptoms already mentioned and usually ascribed to lues and which cases were not luetic, while cases in which hardly any or no symptoms existed have been shown to be positive cases of lues as evidenced by both positive Wassermann and luetin tests. This is not intended to argue that the disease is less frequent than believed (because the writer's opinion is that it often goes unrecognized) nor is it intended to give the impression that lues is more prevalent than ordinarily admitted, but simply to impress the point not to be too eager to diagnose lues without sufficient corroborative evidence, and on the other hand not to be too anxious to exclude the disease without sufficient deliberation and investigation.

Unquestionably the earlier the diagnosis is made and the disease recognized the better chance has the patient by the prompt and proper treatment.

It is evident that since there is difficulty in securing a frank acknowledgment of the disease in the parents, and since the absence of all, or presence of only a few of the symptoms usually attributable

to lues may not be sufficient to exclude the disease, and since the presence of one or more of the symptoms usually found in the disease are not sufficient to stamp the patient as beingluetie, other means by which all doubt may be removed should be employed, if available, in order to recognize the existence of the disease.

Fortunately within the past few years there have come to our knowledge certain tests which, when properly made, should be sufficient to show definitely not only if the patient is in an active state of lues as shown by the Wassermann but whether the patient is either in an active or inactive state as shown by the luetin test of Noguchi. The diagnosis therefore of lues in the baby can be easily established so that the treatment can be promptly instituted.

Probably no greater problem confronts us at this time even in the presence of our knowledge of the disease, its specific organism, its methods of diagnosis, the available drugs which we know to be thoroughly efficient in its treatment, and the vast amount of work done within recent years by the world's best syphilographers, than the one of knowing when a case is cured. Lues long considered an incurable disease must still require a vast amount more of study before it can be stated without fear of contradiction that it is curable in the strictest sense. Evidence is sufficient to warrant the belief that many cases are cured because of those cases known to be reinfectèd; and surely these instances are incentives to stimulate our hopes for a future uniformity in the cure of the disease; yet with our knowledge of the activity and inactivity of the disease, of its latency in an individual for months and years, we must bear in mind the possibility of the cases of reinfection as occurring in those individuals in whom the disease may have been latent and in whom there are no reactive bodies in the free circulation to meet the invasion of the spirochetæ pallidæ and thereby prevent the reinfection.

At least we have the means by which the disease may be controlled and held in abeyance (inactive, and possibly, though unproved, cured). In time, after the examination by autopsy of a great number of cases said to be cured and in which careful records have been kept, will cures be proved and the proper treatment determined. Until then a cure can not be considered positive beyond question.

However, in view of our comparatively recent knowledge in the diagnosis of the disease, of our ability to determine at least its

activity, of our means to produce its inactivity and of maintaining it so, we should be greatly encouraged to further investigation leading to the ultimate perfection in the treatment of the disease with its uniform and positive cure.

In a general way the aims in the treatment of lues should be:

1. To destroy the *spirochetæ pallidæ* in the circulation.
2. To prevent the organisms from becoming surrounded by infiltration and thereby removed from the circulation and protected from the influence of spirocheticides, resulting in latent cases or so-called cures.
3. To promote the absorption of the infiltration or the fibrous character of the lesions surrounding the spirochetes.

The methods by which this should be accomplished are: 1. The administration of drugs to destroy the organisms in the body: (a) by germicidal effect; (b) by increasing the resistance on the part of the individual in promoting the reaction to the organism. 2. The introduction of antitoxin through the mother's milk for same purpose as (1). 3. The administration of drugs to cause an absorption of the infiltration or fibrous lesion surrounding the *spirochetæ pallidæ* placing them in the circulation so that they may be acted upon by (1) and (2).

The drugs employed in the treatment of lues in the baby are mercury, arsenic and iodine. 1. The mercurials most frequently used are calomel, gray powder, biniodide of mercury, bichloride of mercury, and mercurial ointment. 2. The arsenic preparations used are salvarsan, and neosalvarsan. 3. Iodine in the form of sodium iodide, potassium iodide and syrup iodide of iron.

The methods of employment of these drugs are: 1. By mouth; 2. On the skin; 3. Intramascularly; 4. Intravenously.

The drugs given by mouth are calomel in doses of 1/20 to 1/10 gr. three times daily; gray powder 1/2 gr. at the same intervals; or bichloride of mercury 1/200 to 1/100 gr. and the biniodide of mercury in the same dosage. The iodides, always well diluted, 1 to 2 grains, from 6 months to 1 year, three times a day, and the syrup of the iodide of iron 3 to 6 drops three times a day for the same ages.

On the skin mercurial ointment is used for the general treatment in doses of from 10 to 30 grains daily, increasing to the point of tolerance. The employment of this method of administration of mercury is probably the most efficient in children. For the severe pustular rashes baths with from 5 to 10 grains of bichloride in five

gallons of water daily may be used. Calomel with zinc oxide, equal parts, with twice the quantity of starch on the sores on the buttocks is sufficient, in which cases also black wash may be used. Calomel may be used on the condylomata.

Intramuscularly the use of salvarsan has been discontinued because of its irritating effect and because of its causing necrosis of tissue. Neosalvarsan of the two is to be preferred by this method and when used should be given in benzoïnol. Bichloride of mercury, mild chloride of mercury and benzoate of mercury are also employed intramuscularly though not as frequently as mercury on the skin.

By far the best drugs and methods beneath the skin are salvarsan and neosalvarsan, the former in doses of .01 gram for each kilogram of body weight, and the latter in doses of .015 for the same weight. It is preferable not to expose the veins, the drugs being given through the veins of the scalp, the external jugular veins and through the fontanel into the longitudinal sinus.

For convenience the treatment of lues in its relation to the baby should be included under the following headings:

1. Treatment of parents until *cured*.
2. Treatment of pregnant mother.
3. Treatment of nursing mother.
4. Treatment of baby.

1. In the first group are included not only parents before conception but all individuals as well who are infected with lues because we do not know when they may become parents. The disease should be recognized as early as possible and vigorously treated at once as it is in these instances that complete cures are more likely to occur due to the destruction of the spirochetes before they become encapulated in infiltrated or fibrous organized areas. No individual should be considered inactive or cured until observations over a prolonged period show negative Wassermanns not only in the blood but in the cerebrospinal fluid as well.

2. The pregnant mother if detected to have lues should be given the proper and prompt treatment so that her offspring will be brought to term and in a healthy condition, the fetus probably deriving the benefit of the treatment of the mother: first, by the anti-toxin of the mother; second, by the influence of the drugs in the

mother, and third, by the promotion of the resistance of the disease upon the part of the fetus by either of the other two.

3. The mother of a luetic child is herself always luetic as has been shown by many observers, including the writer,<sup>1, 2</sup> the explanation of the origin of the law of Colle being founded on the fact that the mother giving birth to a luetic child does not usually show the classical symptoms of the disease and is therefore considered non-luetic. She is luetic, however, as is shown by the Wassermann and luetin tests. The treatment of the pregnant mother and the nursing mother should be vigorously instituted with the hope of developing in them either a diminution of the virulence of the spirochetes by the administration of drugs, or, an increased resistance of the individual to the disease; the antibodies in the case of the pregnant mother possibly being carried through the placental circulation and thereby offering resistance to the organisms in the fetus; and in the nursing mother the probability of introducing the antitoxin into the baby through the milk. This latter has been the explanation as offered by Ehrlich in the instances reported wherein the administration of salvarsan to the nursing mother resulted in the apparent cure in the suckling baby. A few of these cases had been recorded and were included in a previous paper when the writer reported such an instance.<sup>3</sup> While results have not been uniform by this method of treatment, the occasional beneficial results obtained should warrant its practice in helping the baby, as it is possible that in some instances the treatment of the mother may result in the liberation of sufficient amounts of antitoxin to produce these exceptional results, while in other instances only a little antitoxin may be given the baby through the milk. It may also be that in many instances there may be none eliminated by the breasts. However, if it is possible that some antitoxin may be given the baby in this way in some cases, this method, whenever possible, should be combined with the others more universally used even if for no other reason than that of helping the mother alone.

4. The treatment of the baby should always be instituted as early as is possible and as soon as the diagnosis is made.

#### AUTHOR'S METHOD

As soon as it is ascertained that a woman, known to be or to have been luetic, is pregnant, treatment is advised to be instituted at once,



combining salvarsan or neosalvarsan with mercury and the iodides, and when the baby is born it is determined, as soon as possible, by clinical and laboratory evidences, employing both the Wassermann and luetic tests, whether or not he is luetic. If the baby is negative he is closely watched and subsequent examinations are made. If the baby is positive the baby and mother are both given salvarsan or neosalvarsan, and the mother mixed treatment, and the baby mercurial rubs. There are times, however, when because of the surroundings, medication by mouth is employed instead of the rubs in which instances calomel or mercury with chalk is given. Occasional Wassermann tests are made to determine when the patient becomes inactive or apparently cured at which time the treatment is stopped but observations continued. There are times when it becomes necessary to discontinue medication in the baby owing to the overaction of the mercury, because of gastrointestinal symptoms or loss of weight. After the symptoms subside, the treatment is begun again.

It has been my custom for many years to employ the rubs in the same place; namely, over the belly, without producing any skin irritation. The plan is to bathe the baby with soap and water, thoroughly rinse the skin particularly over the belly, to dry it thoroughly, rub in the ointment, and put on a flannel binder. This procedure goes on daily, employing the same binder. At the end of a week's time the dose of the ointment is increased and the binder changed. In this way it can readily be seen that the daily dose of the mercury is increased. This is done until the point of tolerance is reached.

Salvarsan or neosalvarsan should preferably be given intravenously. Many veins may be used depending upon the individual. A satisfactory vein should be selected either at the bend of the elbow, the jugular vein, the veins of the scalp, or through the fontanel into the longitudinal sinus. The latter offers a favorable site for infants with open fontanels. In giving the drug intravenously, particular care must be exercised because should there be any infiltration, damage may be done to the tissues infiltrated. It becomes necessary, therefore, if the patient is unmanageable to employ an anesthetic. It is preferable to give the drug intravenously, and without an anesthetic, if possible, as the discomfort incident to the anesthetic is then eliminated. In treating the older cases the important question arises whether it is better to give an anesthetic or not. Unless the patient be a suitable one, one able to appreciate the difference

between pain and sensation, and one manageable and in whom no psychic shock will be produced, an anesthetic should be used. It is the writer's firm belief that many nervous systems receive psychic shocks in early life which form permanent impressions and from which the nervous systems never recover. Hence the advisability, whenever necessary, to administer an anesthetic as it will not only be better for the patient but also for the technic of the operator.

The drug should be given preferably without exposing the vein, but when this is impossible the vein should be exposed and the drug given as for intravenous infusion.

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## THE SANITARY ATTACK UPON SYPHILIS\*

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SYPHILIS is perhaps more completely known than any other disease. All of the essential facts which are necessary to an intelligent sanitary attack upon a disease are known concerning it. We know its cause and the conditions under which it is transmitted; we have precise methods for its diagnosis in all stages; we have specific measures of treatment which rapidly control its infectiousness; we can reproduce it in animals, and thus can study any question relating to it under exact experimental conditions. In these facts we have at our disposal the means for an overwhelming sanitary attack upon the disease.

If syphilis were purely a medical problem, its sanitary control would be easy—would compare in ease and effectiveness with the attack upon yellow fever, and would present fewer difficulties than typhoid fever or tuberculosis. The trouble is, of course, that syphilis is not merely a sanitary problem; it is a social problem, in the solution of which we become immediately involved in that most difficult of social questions—the regulation of the relation of the sexes.

Strive as we may to avoid the issue, we are constantly confronted by the fact that syphilis is in the main a venereal disease, and it accordingly affects man in his most intimate social relations. He holds it as a secret disease, and the victim of it makes every effort to conceal it. The secrecy with which syphilis and the other venereal diseases are held—and naturally are held—presents one of the great practical difficulties in carrying out any sanitary campaign against these diseases. This has to be borne in mind in any practical consideration of the sanitary measures which can be used against syphilis.

The sanitary attack upon syphilis includes two sorts of measures:

A. Measures looking to the control of the infected.

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B. Measures which provide safeguards against the dangers of infection.

A. Under measures looking to the control of the disease come:

1. Public health regulations; all measures of restriction of the infected individual—isolation, quarantine, notification of cases, the regulation of prostitution, legal punishment for the transmission of the disease, restriction of marriage.

2. The therapeutic attack upon syphilis in order to minimize its infectious dangers.

#### I. PUBLIC HEALTH REGULATION OF SYPHILIS

Measures which look to the restriction of the liberty of syphilitics as a sanitary measure are impractical because of the secret character of the disease, the long duration of its infectious period, and its wide prevalence. There are probably five million syphilitics in the United States; ninety-nine per cent of them determined, if possible, to keep their disease secret. In the face of such a situation as that, social measures for the restriction of the liberties of syphilitics, much less isolation or quarantine, will manifestly prove futile. You cannot indict even one-twentieth part of a nation; especially if that twentieth part permeates all classes of society and is animated by unanimous determination to keep its misfortune secret.

*Notification.*—There is a strong pressure upon the part of sanitarians to make syphilis a notifiable disease. If it were possible to quarantine the syphilitic until his infectious lesions were passed, the argument for notification as a sanitary measure would be conclusive. But until notification is necessary in order that the public health officials can take the individual syphilitic in charge and restrain him until he has passed his dangerous stage, it will, I believe, prove harmful. In the first place laws requiring notification would not give us the knowledge of the prevalence of the disease which is one of the chief arguments for notification. Laws which affect objectionably a very large body of the community and which at the same time are not strongly supported by public sentiment are ineffective. Without pretending to expert knowledge in the domain of law, I believe this is beyond question; and laws for the notification of syphilis certainly come within this class. We have now laws in eleven states or more pretending to call for the notification of syphilis, some of the statutes requiring even the identification of individuals. All of these laws are dead letters. Statistics based upon

them would be laughed out of any scientific court. They are manifestly so incomplete and so unreliable that they are of no value in any consideration of syphilis, or as a basis for any sort of action against the disease.

But, in the sanitary attack upon syphilis, there are much stronger reasons against laws for the notification of syphilis. In any effective therapeutic attack upon syphilis—and in the therapeutic attack lies our great hope for controlling the disease—the cooperation of the syphilitic must be invoked, and in large part obtained. If it is to be successful, opportunities for diagnosis and treatment must be placed along the lines of least resistance for the patient. He will not cooperate to the fullest extent, if access to these is made difficult or objectionable; and one of the most objectionable things you can do to the syphilitic is to make his secret known. It may be contended that the records of departments of public health can be kept as private as the records of a doctor's office. I do not believe that is true, but I will not stop to argue about it. The syphilitic at least does not want his disease to become a matter of record—and I can sympathize with him in this attitude. In the absence of great benefits to be obtained in the fight against syphilis by notification, I believe those sanitarians who on general principles are urging that syphilis be made a notifiable disease are making an effort that, if successful, would prove a great obstacle to the effective administration of the measure in which lies our greatest hope for diminishing the ravages of syphilis—a thorough-going therapeutic attack upon the disease.

*Regulation of Prostitution.*—The sanitary regulation of prostitution, and the medical examination and certification of prostitutes, need no consideration. Even as sanitary measures they are completely discredited, and they are intolerable.

*Criminal Infection.*—Whenever one sees an innocent person knowingly infected by a syphilitic the criminal character of the act suggests itself. Accordingly, it is a common suggestion that conscious transmission of syphilis to an innocent person should be regarded by the law as a crime and subject to punishment. There could be no question of the justice of such punishment, but in the sanitary attack upon syphilis I believe such laws would be of negligible value.

*Restriction of Marriage.*—The question of the marriage of syphilitics is a more practical one, and a much more difficult one. Undoubtedly syphilitic individuals in the early course of the disease

should not marry. But the question of the marriage of late syphilitics is a much more open one and should not be arbitrarily or dogmatically treated. The laws which have been attempted upon this subject thus far are not only useless from the standpoint of sanitation, but they are in my opinion ill advised and mischievous.

## 2. THE THERAPEUTIC ATTACK UPON SYPHILIS

An organized public effort to furnish the freest possible provision for the treatment of syphilis is justified as a public health measure, because of the great reduction in the dangers of infection which come from treatment of syphilis during its early course. The last few years have demonstrated that by thorough early treatment the infectious lesions of syphilis can be almost wiped out, and their duration in over ninety per cent of the cases brought down from a year or more to a few weeks. This means that the dangers of syphilis to the community could be reduced to a very small fraction of what they now are, if it were the general rule that syphilis is vigorously treated during its early course. The effectiveness of early treatment is so great against the contagiousness of syphilis that it offers us a means by which, under organized effort, the practical extinction of syphilis is within our view as a sanitary possibility. And the therapeutic attack upon syphilis is one which gives results commensurate with our efforts, however small they may be. Every syphilitic treated thoroughly means the almost immediate removal of one of the causes of the spread of the disease. Every prostitute treated promptly means the prevention of many cases. Any effort in this direction, therefore, is well rewarded by results, and this fact should prevent discouragement, because efforts in the beginning must of necessity be small. The prospects of benefit from a large, well-organized effort is hardly to be exaggerated.

To obtain the full benefit of a therapeutic attack upon syphilis would require that the plan be applied on a very large scale, and that free treatment be provided by the state as a sanitary measure. In spite of the extent of syphilis, such an undertaking would not be of colossal proportions. The early syphilitic, the one who, for the protection of the public, needs treatment, is not bedridden; he is usually not even ill or estopped from his occupation. Adequate treatment of syphilis in its early course can be carried out upon ambulant patients. This measure would not, therefore, require the provision

of large hospital facilities for syphilitics. It would require an extensive system of dispensaries to which access is free, easy, and unquestioned. This organized work for syphilis must be offered to the syphilitic in a way that he will accept it. It is this fact that would make compulsory notification, in the present extent of the disease, so great an obstacle to the sanitary attack upon it.

Before we can hope to get the state to make a general attempt at the treatment of syphilis, it will be necessary for the institutions we now have to develop as fully as possible this plan of attack upon syphilis, and establish by practical experience its value. To that end efforts should be made now to convince existing hospitals and dispensaries of their responsibility to the public in this respect, and to influence them to make adequate provisions for the treatment of syphilis. Municipalities also should have brought home to them the importance of establishing facilities for the adequate treatment of syphilis. Emphasis is placed upon *adequate* provisions because adequate provisions are what is now lacking. Provisions of a certain sort now exist to a considerable extent—to an extent quite sufficient to furnish the necessary object lesson in the value of the sanitary attack we are now discussing, if only these existing provisions were adequate.

What the essential conditions are for adequate service of this sort have been very ably discussed by Dr. Michael M. Davis,\* the enlightened Director of the Boston Dispensary. The essentials in Davis's opinion, with which I entirely agree, are: skilled medical service, with salaried medical men; adequate equipment for diagnosis and treatment; a well organized clinic, which provides a follow-up system for patients and social service; provision for evening clinics; and an organization which will not only treat the destitute, but will provide also for those who are able to pay small fees. These conditions are not utopian. They are not excessively expensive. Indeed, in most respects they are not above the standards which are now expected of well organized hospitals and dispensaries.

The first step in this plan is to provide easy and satisfactory opportunities for treatment for the syphilitics who voluntarily seek it. We have sufficient experience now to say that most syphilitics will avail themselves of the opportunity for treatment, when they

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\*For a full discussion of the subject one can refer to his papers in the *Journal of the American Medical Association*, December 4th, 1915, and in the *American Journal of Public Health*, April, 1916.

know where good treatment can be obtained and where knowledge of their condition will not become public property. The next step would be to make an effort to see that treatment is given to the careless and vicious who would not voluntarily seek it. Many of these would be discovered among those who made only one or two dispensary visits. They could thus be spotted for the enforcement of any enactments that are looking to the compulsory treatment of such cases. Prostitutes as a rule avail themselves of efficient treatment if they only know where to find it. In the case of unquestionable prostitutes, I would be glad to see laws compelling them to undergo treatment during the active period of the disease.

Dispensaries such as we are now considering would be intended only for the destitute and for those of small means; but as a matter of fact well equipped and efficiently conducted institutions of this sort would appeal to a very considerable part of the community; and they would compel the physician to see to it that their handling of syphilis equalled in efficiency that of the dispensaries. The efficient handling of early syphilis now is a special job. In the hands of the average practitioner it cannot be done as well as it would be done in a well organized dispensary, and dispensaries of this sort would do much to raise the standard of treatment of syphilis in private practice. They would thus help to relieve the situation to a considerable extent even in the supposedly more fortunate classes which they would not directly reach.

One of the collateral benefits which would accrue from a well organized therapeutic attack upon syphilis would be the educational advantage which the emphasis thus thrown upon the disease would have in instructing both the public and the medical profession. The public would quickly learn from it the importance of early diagnosis and treatment of syphilis. It would remind the physician, too, not only of the importance of precision in diagnosis and of early treatment, but of the fact that the public realized this. Such organized facilities also would perform a very valuable function in furnishing to medical students and physicians proper opportunities for the study of syphilis.

As a part of the propaganda for efficient treatment of syphilis, there is one matter upon which those interested in the control of the disease should exercise their influence; and that is in urging the importance of adequate training of physicians in the subject of the



venereal diseases. It is of the highest sanitary importance that the physician should be able to recognize venereal diseases early and treat them efficiently. It is no secret that competent knowledge in the diagnosis and treatment of venereal diseases is not widespread among us now. This is not to be wondered at. The diagnosis and treatment of syphilis and the other venereal diseases requires special technical knowledge that is not now thoroughly given the medical student in his routine course. The teaching of venereal diseases in our medical schools is superficial and incomplete. It is a situation which should not exist, and which all organizations interested in the control of venereal diseases should use their influence to correct.

B. Under measures safeguarding against the dangers of infection come:

1. Measures to prevent indirect infection.
2. Education of the public as to the risks of syphilis and the methods of its transmission.
3. Instruction of the infected in order to lessen his danger to others.
4. Methods of preventing infection when contact with infected individuals occurs; personal prophylaxis of syphilis.

#### 1. PREVENTION OF INDIRECT INFECTION

The dangers of indirect infection of syphilis through the common use of personal articles has become generally known, thanks to the educational campaigns of recent years. Excepting hereditary syphilis, the cases of syphilis which compel our sympathy most are those which we see of accidental infection. These cases constitute hardly more than five per cent of the entire number, and by far the greatest number of them in my experience are among doctors. Extragenital infections outside of the professions that care for the diseased are much less common, but they are sufficiently frequent to warrant the efforts to educate the public to the dangers of the common use of personal articles, and to prevent the opportunity for the use of such articles in public places. This constitutes the easiest problem in the sanitary attack upon syphilis, and its consideration need not detain us now.

## 2. EDUCATION REGARDING SYPHILIS

The education of the public as to the risks of syphilis and the methods of its transmission are a part of the sanitary attack on it, but it constitutes a difficult problem; difficult not more on account of the sexual facts involved than on account of the difficulty in sufficiently emphasizing the importance of syphilis without magnifying it. A temperate statement of the dangers of syphilis is a difficult feat. My impression is that the public is already very widely acquainted with these dangers; that, in fact, that part of the public which can be reached in any educational campaign has a morbid dread of syphilis and an exaggerated notion of its terrors, rather than an attitude of indifference towards it. So true is this that an unreasoning fear of syphilis is not uncommon among those who are free from it; and among the infected the average syphilitic patient suffers, I believe, as much or more from the knowledge of having the disease as from the disease itself. This applies not only to the refined educated classes, but to the ordinary man. And one of the difficulties which men who treat syphilis have to combat is this morbid dread of the disease. Syphilis is a serious disease, but so is syphilophobia. I do not wish to minimize the seriousness of syphilis, but I wish to call attention to the damage which is done by exaggeration in the campaign of education against syphilis. I have known a good woman, who did not have syphilis, to go home and turn on the gas and kill herself, because she feared she had it. And her case is but an extreme illustration of innumerable cases of morbid fear of syphilis that one sees. In our educational campaign against it there are the strongest reasons for temperance and restraint. I believe plays like "Damaged Goods," movie shows portraying the horrors of the venereal diseases, and alarmist articles on syphilis, whether purporting to be scientific or popular, produce a great deal more suffering than they do good.

What can be done by intelligent devoted work in educating against syphilis and the other venereal diseases is shown by such organizations as the Oregon Social Hygiene Society. The work of such organizations pays for itself many times, not only in saving many young people from venereal diseases, but in the moral stamina which it promotes. I believe, however, that experience shows that too much cannot be expected of education. It is, in my opinion, a valuable,

but by no means our most effective weapon in the fight against the venereal diseases.

### 3. INSTRUCTION OF THE INFECTED

The need is manifest of the instruction of the infected as to his dangers to others and the precautions he should observe in order to minimize these dangers. Such instruction, of course, should be a part of the management of every patient in the active stage of syphilis. It is observed by the intelligent and conscientious, and neglected by the stupid and careless and vicious. It constitutes one of our weakest weapons of sanitary attack.

### 4. THE PERSONAL PROPHYLAXIS OF SYPHILIS

The real problem in guarding against the dangers of infection with syphilis is that of protecting the individual from the danger arising from sexual contact with syphilitics. Sexual contact causes ninety to ninety-five per cent of syphilis. Were it not for this method of transmission, syphilis would soon cease to exist. As long as syphilis is prevalent, there is the strongest ground in the sanitary attack upon syphilis to do everything possible to minimize the dangers of infection when actual contact with syphilis occurs. In Metchnikoff's method of prophylaxis, by the use of calomel ointment we have a means of personal protection which has proved its value. It is not sure, but it greatly diminishes the chances of infection, and, if men are going to expose themselves to syphilis, they should, for the protection of others as much as for the protection of themselves, know of this comparative safeguard. How to disseminate this knowledge is a delicate question. Men certainly should not be taught that it is an infallible preventative. It is not; and they should thoroughly understand that it does not banish the risks. But the partial protection which it offers should become a part of the common knowledge of the adult population. I do not believe it is knowledge which should commonly be given to boys, but that no boy should have it, I believe, is not true. Fathers should know it, and with them should be left the responsibility of individual cases. Among large bodies of men, such as armies and navies, where exposure of a great many of them is certain, and where methods of personal prophylaxis can be carried out, the withholding of the benefits of it is, in my opinion, nothing less than a sanitary crime.

The foregoing is a brief summary of the means which we have available for the sanitary attack upon syphilis. The two most important measures are the therapeutic attack upon syphilis, and personal prophylaxis. In these we have measures of first class importance. When they obtain widespread adoption, we will, I believe, be able to throttle the disease. Until we avail ourselves of their benefits, syphilis will remain beyond our control.

In this consideration I have confined myself to the subject of syphilis, in order to be definite and as brief as possible, but, as a matter of fact, all that has been said upon syphilis applies with little or no modification to gonorrhea and chaneroid. The problems of all the venereal diseases can be handled as one problem and in the same institutions.

## THE TEACHING OF SYPHILIS

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ONE of the great problems before the medical profession is the proper teaching of syphilis. Fortunately this fact is generally recognized. The discussion of Dr. Irvine's paper read last June before the Section on Dermatology of the American Medical Association, bears witness to this, even if the general alertness of the men teaching syphilis would not suffice to do so. The great changes and advances in knowledge concerning the "black plague" have aroused a widespread interest in the disease and the medical profession is reacting promptly.

In a journal devoted to syphilis it is totally unnecessary to call attention to the prevalence of the disease. The many papers reporting the results of routine Wassermann reactions in our large hospitals have already covered this point fully; suffice it to say that the great prevalence of syphilis, both external and internal, is now being generally recognized by those doing hospital work.

That there is a real need for the better teaching of this disease is proved by several facts: the men who are doing the teaching are eagerly grasping for more time to devote to the subject; at present in the majority of the medical schools there is not enough time or material to properly instruct the students in the many phases of the protean disorder: upon this point we need only the testimony of the teachers.

That syphilis in the past has not been properly treated is proved by the large number of intelligent men who develop tabes, paresis, and various other visceral manifestations, not to mention late cutaneous lesions.

In an attempt to ascertain how syphilis is treated in private practice, I have just finished an analysis of 59 private patients seen in the last two years. Many of these syphilitics had been treated by

more than one man, and have almost always had some good and some bad therapy. Where this is the case, they have been included among those badly treated.

Cases properly treated.....	15
Cases badly treated.....	25
Cases fairly well treated.....	15
Cases untreated because early.....	4
Cases with early diagnosis.....	31
Cases with late, or wrong diagnosis.....	28

Undoubtedly, outside of insufficient treatment, the great error in handling these cases has been the failure to use the dark field illuminator at the time of the primary sore; in only one case out of nine primaries had this been done, and then the organism was not found, although at the time he consulted me it could easily be demonstrated. Then, too, there is considerable confusion between the skin manifestations. Hardly a week passes that I do not have to pass upon a case of pityriasis rosea, seborrheic dermatitis, or drug rash that some one has considered specific. All neurologists know that the central nervous manifestations are too frequently not recognized until considerable damage has already occurred. The failure of the men practicing medicine to recognize syphilis should be put squarely where it belongs, upon the medical school.

Having shown that a need for better teaching exists, the problem must now be put. It has well been said that to know syphilis is to know the entire field of medicine, for syphilis may attack any organ of the body, and may simulate or be simulated by nearly every known disease. The chancre may occur upon any exposed surface, and may resemble many lesions, including cancer; the early skin manifestations are similar to those of a dozen benign diseases, and the same is true of the later manifestations. Syphilitic affections of the hair and nails may closely resemble various other affections, which require totally different forms of treatment. Luetic manifestations upon the mucous surfaces of the mouth are frequently not recognized by the inexpert, and I know of several cases that have been submitted to operation, when antisiphilitic treatment was all that was necessary. In other words a dermatologist could frequently have saved much trouble. But the reverse is often true: affections of the digestive tract that are due to syphilis require the aid of a good internist in making a proper diagnosis, and the same is true of gummata of the lungs, of various forms of heart disease and arteritis, as well as other

affections of the circulatory system. Frequently there is doubt as to whether nephritis is due to mercury, syphilis, or some other cause. Syphilitic disease of the central nervous system or of the glands of internal secretion frequently demand the services of a neurologist, the eye lesions often are difficult to recognize. I have seen eminent oculists not in accord upon a case of retinitis occurring in a syphilitic. To properly interpret bone and joint lesions demands a radiographer, while the laboratory man is indispensable for the performing of the Wassermann. If one department is to handle all cases of syphilis without consultation, either the man in charge must thoroughly know every field of medicine, which is now practically impossible, or in the department must be included a dermatologist, an internist, a neurologist, a surgeon, a radiologist, and a first-class laboratory man. In order that students may be properly taught syphilis, they must be under the joint instructions of dermatologists, internists, pathologists, and various other specialists. It is generally admitted that the early diagnosis of syphilis is of the utmost importance, so it is essential that they learn the use of the dark field illuminator to discriminate between chancres and chaneroids; they must have a grasp upon the essential pathology of the disease; they must learn the triumphs as well as the limitations of the Wassermann reaction as well as the other laboratory tests upon the spinal fluid. It is absolutely essential that they be able to discriminate between the cutaneous eruptions, and they must understand what visceral diseases syphilis may cause or resemble.

Now that the problem has been stated let us inquire as to how it may be met, for met it must be if we are to do our duty by the public. Harvard and Johns Hopkins have established special courses in syphilis under the charge of one man. The result of this has been to arouse a great hue and cry among dermatologists, who feel that they are being deprived of one of their special prerogatives. And yet it seems to me that the dermatologists have only themselves to blame, for if their courses had met all of the demands there would be no call to make such changes. From visits to many clinics it may safely be stated that until a comparatively recent date the dermatologists were laying stress simply upon the dermatological aspects and the treatment of syphilis, and almost totally ignoring all other points of view; the students were never told that every person suffering from late syphilitic lesions should have his heart and aorta

examined, not to mention his nervous system. The solution of having the entire subject handled by one man would be proper and easy if a Fournier or a Hutchinson could be picked up in every school, but this is certainly not possible. It also would take years to develop any one man so that he could absolutely recognize all of the manifestations of syphilis. As a result it is clearly impossible to have all phases of syphilis taught by one man, or in one department, unless that department be very large and very excellent.

However, there is one solution of the problem that is essentially practical. One man should be able to cover the general course of syphilis; he should deal with the history, the occurrence, the economic importance, the etiology, the clinical course, and certain of the clinical manifestations. The other lesions induced by lues should be taught in the other departments to which they naturally belong, lesions of the eye, by the oculist, and so on. There should be correlation in the time of teaching of these manifestations as Corlett has long ago suggested.

Now, who should be the man to handle the general subject? If the genitourinary specialist handled it, he could deal only with the genital chancre and with the relatively infrequent late manifestation of the urinary or genital organs. The internist could cover only the lesions that were not visible to the eye, and the lesions that were almost uniformly of late development, and the other specialists could cover with authority the lesions developing in their particular fields. Inasmuch as the early lesions of syphilis are almost invariably superficial, and inasmuch as the most important time to make a diagnosis is early, the dermatologist would seem to be the logical man to handle not only the general subject but also the various early lesions, such as the initial lesions, and the affections of the skin and mucous membranes; in other words he could cover more of the subject with authority than could any other man. In practice this has been found to work well. Many dermatologists have become great syphilologists. Who can forget Neisser, Fournier, Hoffmann, Unna, Auspitz, Kaposi, Hallopeau and many other eminent men abroad, not to mention the great work of Fordyce in our own country.

In attempting to learn how other schools have solved their own individual problems I have written a number of men, and have had replies from Alderson, of Leland Stanford, Dyer, of Tulane, Schamberg, of the Philadelphia Polyclinic, McEwen, of Rush, Cole, of



Western Reserve, Wile, of the University of Michigan, Irvine, of the University of Minnesota, Zeisler, of Northwestern, McDonnell, of Yale, and Sutton, of the University of Kansas. Of these, the University of Michigan is the only school that has a special department of Syphilology although Wile also handles the subject of dermatology. In all of these schools stress is laid upon the clinical teaching. The use of the dark field illuminator is emphasized in all, as well as the technic of salvarsan administration. The majority of the men feel that the teaching could be bettered by the creation of a special department of syphilology, of whom the head should be a dermatologist. All feel that all syphilitic cases should be sent to this department for treatment. Irvine writes me: "Treatment of *all* cases should be centralized in one clinic, one man seeing all cases, if possible, and directing treatment in each case; this personal contact does much to retain cases. Clinic should have sufficient equipment of instruments. Clinic should have sufficient rooms so that each patient can be talked to and treated privately. Patients should under no conditions be allowed to see and carry around their own records. Clinic should have own laboratory for Wassermanns and spirochete examination and animals for experimental work. Clinic should have sufficient assistants and nurses so that each patient may be given enough time, this not only impresses the patient of the seriousness of the disease but cannot fail also to impress the student in contrast to the hurry up order of things. Some arrangement should be in force whereby it is possible to administer salvarsan or neosalvarsan in infectious cases whether they have the money to pay for it or not. Records in most clinics show that many patients appear but once and they should not be allowed to leave without treatment. I believe that this is best done by charging a small profit to those who can afford it and using the surplus to pay for others. Clinic should have a sufficient number of beds at its disposal to confine infectious cases and do intraspinal work. Clinic should have adequate social service; from a public health standpoint no clinic can even hope to do this work without this department. Patients should be furnished with literature apprising them of the seriousness of their disease and the importance of its treatment."

Now as to the solution of the problem in the Howard Medical

DEPARTMENT OF THE INTERIOR  
FREEDMEN'S HOSPITAL  
Out-Patient Department

Name \_\_\_\_\_ Age \_\_\_\_\_ Date \_\_\_\_\_  
Address \_\_\_\_\_ Sex \_\_\_\_\_ S. M. W. \_\_\_\_\_  
Race \_\_\_\_\_ Birthplace \_\_\_\_\_ Occupation \_\_\_\_\_

## SYPHILOLOGY

Diagnosis \_\_\_\_\_  
History taken by \_\_\_\_\_  
Patient's complaint \_\_\_\_\_  
Use of alcohol \_\_\_\_\_; of tobacco \_\_\_\_\_  
Home conditions \_\_\_\_\_  
Working conditions \_\_\_\_\_  
Condition of spouse \_\_\_\_\_  
Children: Living \_\_\_\_\_; dead \_\_\_\_\_; miscarriages \_\_\_\_\_

## PAST HISTORY

Age at time of infection\_\_\_\_\_How acquired\_\_\_\_\_

Site of initial lesion\_\_\_\_\_

Treatment of initial lesion\_\_\_\_\_

Appearance of secondaries\_\_\_\_\_

Location\_\_\_\_\_Skin\_\_\_\_\_

Hair\_\_\_\_\_Glands\_\_\_\_\_

Mucous membranes\_\_\_\_\_Joints\_\_\_\_\_

Remarks \_\_\_\_\_

Treatment of secondaries\_\_\_\_\_

\_\_\_\_\_

Appearance of tertiaries\_\_\_\_\_

Character of tertiaries\_\_\_\_\_

Treatment of tertiaries\_\_\_\_\_

\_\_\_\_\_

## EXAMINATION

Lesion for which admitted \_\_\_\_\_  
 Skin \_\_\_\_\_  
 Mucous membranes \_\_\_\_\_  
 Hair \_\_\_\_\_ Glands, axillary \_\_\_\_\_; inguinal \_\_\_\_\_  
 epitrochlear \_\_\_\_\_; cervical \_\_\_\_\_; mammary \_\_\_\_\_  
 Digestive tract \_\_\_\_\_  
 Liver \_\_\_\_\_ Thyroid \_\_\_\_\_  
 Heart \_\_\_\_\_  
 Aorta \_\_\_\_\_



School. Ten lectures are devoted to the subject of syphilis, and they are arranged as follows:

- I. Introduction. History. Occurrence. Economic Importance.
- II. Etiology. Pathology.
- III. Clinical Course.
- IV. Chancre. Early Cutaneous Lesions.
- V. Late Cutaneous Lesions. Cutaneous Complications. Affections of the Hair and Nails.
- VI. Lesions of mouth and throat, of the respiratory tract and of the digestive tract.
- VII. Lesions of the circulatory organs, and of the bones and joints.
- VIII. Lesions of the genitourinary organs, and of the central nervous system.
- IX. Congenital syphilis. Diagnosis.
- X. Treatment.

The one idea in these lectures is to instill into the students what lesions may complicate syphilis, so that they may be on the lookout for them, and also to teach them that in many different affections syphilis should be excluded.

However, the major portion of the teaching is done in the dispensary, which has a wealth of clinical material, and to which all syphilitic cases, with the exception of the nervous ones, are referred for routine treatment. Special emphasis is laid upon taking a careful history, and making a complete examination, and the history cards are especially devised for this purpose. It is compulsory that patients be handled along the lines laid out in Dr. Irvine's letter. While they have no visiting nurses, they have utilized the Visiting Nurses' Association to take their places. The Wassermann reactions are done in the hospital laboratory, where the students can see the complete technic, and learn how carefully these tests must be made in order to be of any value. The patients are never hurried, and those taking mercurials have their urine and mouth carefully examined at each visit. Each student spends thirty-two hours in the dispensary, and the attempt is made to give as much individual instruction as possible, it being felt that fewer hours and more personal contact is desirable to more hours and less personal instruction.

The above described course is given in the third year. In the fourth year, the students act as clinical clerks in the wards. Inasmuch as syphilitic patients are admitted to the wards, the senior students have an opportunity to see intraspinal work, and to learn the aspects of the visceral manifestations.

## CONCLUSIONS

1. It is essential to have better teaching of syphilis.
2. This teaching should be essentially clinical, and should be done both in the dispensary and at the bedside.
3. To teach syphilis properly the patients must be well handled, as example is the best teacher.
4. The teaching can be done by one department alone, provided that it has a special corps of select men.
5. In the vast majority of instances one man should head the department, and he should work in harmony with the other departments, so that the whole subject can be handled systematically.
6. The dermatologist is usually the proper man to head this department.

## THE PLACE OF SYPHILIS IN OUR MEDICAL SCHOOLS AND HOSPITALS

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THERE appears to be a growing uncertainty in the minds of those who direct our medical schools and hospitals as to the proper place for the teaching and the treatment of syphilis. This has become a very acute question since the discovery of the Wassermann test and the introduction of salvarsan—the “*magna therapia sterilans*.”

During these few brief years the general practitioner and the specialist in all branches of medicine have convinced themselves that they are capable of taking care of syphilis. For them all a previously difficult question has become an easy problem—the Wassermann test will make the diagnosis and salvarsan will do the rest.

Thus these two great modern discoveries have opened anew the old and vexed question as to who is most competent to care for syphilis. Formerly the surgeons claimed this right; then, in the last few years, as has been stated, all medical men wished to exercise this privilege; but now, most recently, a third aspirant to these honors has arisen, namely, the syphilologist. Let it be said, however, in justice to this last group, that the honor is being thrust upon it by certain hospitals and by certain medical schools rather than that this new body of men claims this privilege as its right. In other words, ultramodern minds have conceived the theory that this superspecialism is for the best; in short, that the man who devotes himself wholly to this one disease, to the exclusion of all other medical problems, must of necessity prove the most fit to deal with it as a therapist and as a teacher.

What has been the accepted idea of special medical fitness? Let us answer: long experience based upon a comprehensive knowledge of general medicine plus prolonged and devoted attention to the specialty under consideration and finally a most intimate acquaint-

ance with that branch of medicine most closely allied to the given subject. A man possessed of such knowledge is de facto the most competent to make a correct diagnosis without which, as a firm foundation, all else is futile.

In the past, many of us, holding to these tenets, have been wont to regard the dermatologist as best fitted to diagnosticate and to treat syphilis and to hand on to those who follow his knowledge of the disease. The dermatologist, worthy of the name, must of necessity be well acquainted with general medicine, for it is only the superficially incompetent who can complacently consider skin diseases as independent of the general economy and ignore the etiological role played in certain dermatoses by the hematologic, the digestive, the nervous or the endocrinous systems of the body. Again, the well trained dermatologist must be thoroughly conversant with the various so-called exanthemata and their frequent perplexing variations, and such knowledge is a recognized part of his medical equipment. A physician armed with such knowledge is surely well fitted to cope with the most puzzling of all morbid entities, i. e., syphilis; and in the past this so-called specialist has prided himself upon his special devotion to the study of this disease.

If, therefore, the dermatologist has been true to these special and exacting standards of medical learning, who else in the medical field can be considered worthy to supplant him?

It is because in certain quarters a movement has already been launched and is, perhaps, gaining rapid headway, to divorce syphilis from dermatology that these few notes of warning are sounded.

This movement is headed in one of two directions, to-wit:—syphilis shall stand alone and be treated and taught in a department completely separate from that of dermatology; or it shall be considered a part and parcel of general medicine and as such shall be submerged into this great division of medical science.

One theory might perhaps be considered constructive but the other would surely merit the term destructive; and of the two ideas the well-wisher of the disease would in preference surely vote against the latter. If syphilis were fused with general medicine it might soon lose its special teacher and with this loss would go all the special knowledge, special privileges and special hours now devoted to its study and in the end the world would be the poorer. [Since these lines were written the writer has heard a teacher of neurology

(a subdivision of general medicine in the curriculum) complain that syphilis was accorded in section teaching as much time as that allotted to his whole subject.] Such a step could only be regarded as reactionary.

The other plan, the one we have called constructive, has much in its favor. We moderns believe in specialism, in efficiency. We believe that all branches of human knowledge have increased to such an extent that no one individual can now grasp them all or even begin to, and so we have divided and subdivided and still further partitioned off our mental pursuits and activities until now every smallest part of learning has its devotees, men who have consecrated their lives to these separate trends of thought and the result is our wonderful modern world-progress.

Following these precepts in a purely logical manner one degree still further, at least one hospital decided to separate its syphilitic from its dermatologic patients. This hospital was in the rare position of being able to invite to the command of this new department two men—one, a master of surgery, of dermatology and of syphilis; the other possessed of a sound knowledge of dermatology, of syphilis and of the exanthemata as well. These two enthusiasts added to a splendid clientèle a large following from their former hospital and brought with them a model social service so that today the original solid structure has been increased two fold or more and the present department stands as a splendid tribute to the progressiveness of the authorities who planned it.

So far so good. But what of the future? If all hospitals are to follow this apparently successful venture, what does the movement lead to? The curriculum of our modern medical schools is already so overcrowded with the necessary fundamentals of medicine that the time devoted to the specialties is being curtailed more and more with each succeeding year and even now students must begin their individual clinical careers with an ever-diminishing knowledge of the special branches, dermatology and syphilis of course included. We have endeavored to point out that no man can be a successful dermatologist or a competent syphilologist if he has not had an extensive career in both of these allied branches of medicine plus a thorough acquaintance with the exanthemata. Who else is competent to differentiate between border-line cases of syphilis and psoriasis, of syphilis and variola, of syphilis and annular lichen planus,



of syphilis and pityriasis rosea, of syphilis and dermatitis medicamentosa, of syphilitic gummata and erythema induratum, of chancres or of late syphilitic ulcers and carcinoma, of syphilitic gummata and scrofuloderma, of syphilis and certain types of sarcoma, of syphilis and perforating ulcer, of syphilis and rare types of leprosy, of syphilis and granuloma fungoids, etc., etc., all the perplexities and the niceties of differential diagnosis between syphilis "the great imitator" and many, many other dermatoses. The late Louis Wickham of Paris once told the writer that he intended to begin a book on dermatology, the main idea of the treatise to be a comparison of practically all other dermatoses with syphilis. It is to be regretted that death barred this clever and brilliant idea from its fruition.

In the past, knowledge of these allied subjects was gained by clinical experience in a dermatological clinic. There, examples of the two specialties were encountered together in great numbers and they could be contrasted and studied side by side in the closest communion—the result has been our present generation of able diagnosticians.

But what of the future? Let me cite a recent illuminating experience.

In the ultramodern syphilitic clinic above described, one of the new assistants was shown a widespread and severe eruption of acne necrotica and asked by his superior—a trained dermatologist—what he considered the dermatosis to be. The reply was syphilis, and when the correct diagnosis was given to this possible future head of a syphilitic department he naively remarked that he had never heard of such a disease.

This anecdote seems to furnish an early proof of what the writer has feared from the inception of this super-refinement of specialism, i.e., that if this movement takes firm root the inevitable result will be a new generation of men who know syphilis thoroughly but who are sadly ignorant of dermatology; and of course the same crippling ignorance will surely crop up among our future dermatologists, who will be woefully ignorant of syphilis; and the result will be disastrous to our future patients.

Thus far we have confined ourselves to the clinical side of the question. The theoretical hiatus will also result as sure as fate. If syphilis and dermatology are to be treated in our hospitals as sep-

arate entities, it follows that they must be taught clinically in the same divorced manner and thus our future graduates in medicine will leave our schools with a greatly diminished practical knowledge of these two important subjects.

These, therefore, are the facts as the writer sees them. Is he correct? He leaves the answer to his readers.

# THE IMPORTANCE OF A KNOWLEDGE OF SYPHILIS, AND ESPECIALLY OF VISCERAL SYPHILIS FOR GENERAL MEDICAL DIAGNOSIS

BY LEWELLYS F. BARKER, M.D., BALTIMORE, MARYLAND

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## A. INTRODUCTION

PHYSICIANS before our time had, it is true, a lively realization of the ubiquity and the polymorphism of syphilis, but even the acumen of the most alert diagnostician was not sufficiently keen before the invention of the newer methods of serodiagnosis and spirilodiagnosis to recognize lues in all the places and in all the forms in which it occurs, and in which we are now able to detect it. In the first number of a new journal devoted exclusively to the study of syphilis, it would seem desirable to emphasize the importance of a knowledge of syphilis in the ordinary every-day work of medical diagnosis. The existence of syphilitic infection is most often overlooked either because it is not thought of, or because, though thought of, the relatively easy methods now at our disposal for determining with certainty the existence or non-existence of the disease are not applied, or are applied only very imperfectly.

There is less excuse than formerly for mistakes in diagnosis in connection with the syphilitic diseases. The newer methods of examination that have been worked out have been reported in the medical journals, are filtering gradually into the textbooks used by medical students, and are taught and used by instructors in the medical schools in connection with cases of syphilitic infection. And yet it is matter of concern to medical consultants that they find the disease still often going on for years unrecognized and unsuspected even in patients that are under more or less close medical supervision. For the present, therefore, it is incumbent upon medical teachers vigorously to lay stress on the dangers of such diagnostic oversight and pressing to urge all practitioners of medicine first to keep in mind the extraordinary prevalence of syphilis, and secondly to familiarize themselves with and to apply the serodiagnostic,

spirillodiagnostic, cytodiagnostic, and roentgenodiagnostic procedures that, supplementing the ordinary physical methods of examination, make it, as a rule, easy to say positively whether or not a patient has, or has not, a syphilitic infection.

External syphilis and orificial syphilis are, as a rule, recognized now-a-days by general practitioners. The characters of the syphilitic chancre, of the cutaneous manifestations of syphilis, of the syphilitic mucous patch, of the syphilitic condyloma, of the Hutchinsonian teeth, of the syphilitic interstitial keratitis, and of the syphilitic saddle-nose, are well-known and a knowledge of them has become widely diffused among physicians; these phenomena when observed are usually properly valued and serve satisfactorily as criteria for diagnosis.

Internal syphilis, on the contrary, especially that unaccompanied by external manifestations, goes very often unrecognized, and it is to some of the more obscure forms of syphilis that it is my purpose in the present article to advert.

#### B. SYPHILITIC FEVER

Aside from the fever that often accompanies the eruptive stage of syphilis, we not infrequently meet with a long-continued fever in the later stages of the disease and unless it is known that the patient is luetic, or unless a Wassermann test is made, the nature of this fever may go unrecognized.

Among the earlier reports of this obscure syphilitic fever are those of Courteaux (1871), Musser (1892-3), Monier (1899), Maitland (1899), and Prentiss (1899). Since the attention of the profession has been called to the subject, many cases have been described in this and other countries. In the United States, the article by E. G. Janeway, in which the danger of error in diagnosis between chronic syphilitic fever and tuberculosis was emphasized, and the paper by T. B. Fletcher, in which three cases of syphilitic fever were reported from Osler's clinic, have led practitioners to be on the watch for fever of luetic origin.

Now that we resort to the Wassermann reaction as a diagnostic aid in all obscure cases of the disease, fever of syphilitic origin is far less likely to be overlooked than formerly when, unless the therapeutic test with potassium iodide was thought of, the differentiation of this form of fever from other chronic febrile processes was oc-

casionally embarrassing to the practitioner. To quote from the late Dr. Janeway, "ignorance of the fact that syphilis, in what is termed its tertiary period, may occasion a fever of long duration, malaise, emaciation, perhaps perspiration, also, without of necessity presenting such definite local manifestations, either external or internal, as can be made out on such casual examination as often occurs when a patient seeks advice at the office of a consultant on one or a few occasions, is largely the explanation of the mistakes."

When we think of the difficulties that practitioners of a former generation had to overcome in differentiating among fevers due to malaria, to tuberculosis, and to syphilis, we must be grateful for the new methods that have been devised and which permit us, now, easily to decide, at least in most cases, which of the three we are dealing with.

#### C. SYPHILIS OF THE RESPIRATORY APPARATUS

NOSE AND PARANASAL SINUSES.—Syphilis here is most often found by the nose-and-throat specialist though the general practitioner may suspect its existence and refer the patient to the specialist for examination or to a clinical laboratory for the Wassermann test.

In CONGENITAL LUES, the nose is especially prone to attack. The "snuffles" of the syphilitic child may be the first sign to attract the attention of the physician to the condition.

In ACQUIRED NASAL SYPHILIS, the primary lesion may occur in the vestibule of the nose, on the alæ, or upon the nasal septum. Such nasal chancres are often mistaken for other conditions and only after secondary symptoms appear is their true nature revealed. Where there is any suspicion of luetic infection, scrapings of the sore should be examined for the *Treponema pallidum*.

In the secondary stage of syphilis, the eruption is sometimes visible on the nasal mucous membrane.

In tertiary syphilis, *gummatous infiltrations* with hypertrophic changes in the conchæ are common. Ulceration may follow and may extend so as to lead to extensive destruction of the nasal cartilages and bones. *Ulceration and perforation of the nasal septum* are common. As an end-stage, the sunken bridge of the nose with flattening and widening of the transverse diameter and turning up of the tip of the nose is well-known to all as the "saddle-nose" of syphilis.

Occasionally, ulceration and necrosis extend into the paranasal sinuses or even into the cavity of the skull.

For excellent summaries of nasal syphilis, I may refer especially to the writings of C. H. Knight, J. L. Goodale, and P. H. Gerber.

**LARYNX.**—In secondary lues, a *subacute catarrh* of the larynx is common and, on laryngoscopy, hyperemia, and sometimes papules and superficial erosions are visible.

In tertiary laryngeal lues, *gummatous infiltrations* occur in the submucosa or in the perichondrium. When these gummata soften and break down, punched-out ulcers with firm, reddened margins appear, and, later on, scarring with stenosis or deformity may occur. Hoarseness or pain on swallowing, especially when occurring in a person known to have had syphilis, should always lead one to make a thorough laryngoscopic examination. Laryngeal lues detected early is very amenable to treatment, but allowed to run into the cicatricial stage, the condition often becomes serious and even dangerous to life since fatal laryngeal stenosis sometimes occurs.

**TRACHEA AND BRONCHI.**—In the trachea, *ulceration* and *scarring* at the bifurcation are not uncommon. In the bronchi, *syphilitic stricture* occasionally leads to bronchostenosis, causing dyspnea, diminished expansion of one side of the thorax, and enfeeblement of the breath sounds in the area supplied by the affected bronchus. The roentgenographic appearances of bronchostenosis are characteristic (Jacobsohn; Ziegler). The syphilitic nature of a lesion may be recognizable on tracheobronchoscopy (Hommel), and be corroborated by a positive Wassermann reaction. The review of tracheal and bronchial syphilis made by Lewis A. Conner in 1903 is still one of the best papers to consult.

**LUNGS.**—For a long time it was exceedingly difficult to differentiate pulmonary syphilis from the far more common pulmonary tuberculosis, and, even with the advent of bacteriodiagnostic, serodiagnostic and roentgenodiagnostic methods, differentiation may still, in single cases, be exceedingly difficult. Diagnosis is further complicated by the fact that syphilis of the lungs and tuberculosis of the lungs may occasionally co-exist in the same patient.

In **CONGENITAL LUES**, the white pneumonia (*pneumonia alba*) of Virchow is a lesion occasionally found in the lungs of stillborn children or of children that have died shortly after birth. Still

more common, and sometimes combined with pneumonia alba, is an *interstitial syphilitic pneumonia*. Other signs of congenital lues usually co-exist.

In ACQUIRED LUES, *gummata* and fibrous scarring (*syphilitic fibrosis*) are two principal lesions that occur. In differentiating pulmonary syphilis from pulmonary tuberculosis, certain important facts should be kept in mind:

(1) In syphilis, it is the root of the lung and the central areas that are most often involved, whereas in tuberculosis an apical process is most common.

(2) In syphilis, cavity formation (except bronchiectatic) is rare even in advanced stages.

(3) Bronchostenosis is common in lues, rare in tuberculosis.

Of the symptoms of pulmonary syphilis, the commonest are cough, dyspnea, and hemoptysis.

The physical signs in syphilis of the lung are rarely characteristic enough to give a clue to the etiological diagnosis. When the signs suggest a chronic inflammatory process in the lung and repeated examinations of the sputum are negative for tubercle bacilli, the Wassermann test should be applied. The anamnesis, the careful examination of other parts of the body for luetic lesions, and good roentgenograms may be of help in differentiation. Mycoses of the lung, and neoplasms, may sometimes be confused with syphilis of the lung. For good reviews of pulmonary syphilis, the reader may consult the articles by Fowler, Stengel, Landis and Lewis, Diculafoy and Schlesinger.

PLEURAE.—Pleuritis without effusion has been thought to be due often to lues (Stintzing), but the evidence is not convincing. *Gumma* of the pleura rarely occurs, but it is occasionally met with, and then, most often, as an extension of a gumma of the lung. I have seen one case of widespread gummatous infiltration of this type that cleared up like magic under the administration of salvarsan.

MEDIASTINUM.—Of late, some attention has been paid to syphilis of the mediastinum. Two French theses on the subject appeared in 1913, and, in 1914, Giffin, of the Mayo clinic, reported five cases. Occasionally, it is associated with a pericarditis of luetic origin. It would seem that lues is less important than tuberculosis in the origin of chronic mediastinitis. The symptoms of mediastinal inflammations are well summarized in the review by C. P. Howard (1915).

## D. SYPHILIS OF THE CIRCULATORY APPARATUS

HEART.—In CONGENITAL LUES, a *diffuse interstitial myocarditis* due to the syphilitic infection of the fetus is known to occur.

In ACQUIRED LUES, *gummata* are occasionally encountered in the heart, most often in the septum between the atria, or in the inter-ventricular septum. On account of this site of predilection for syphilis of the heart, the conduction-system is often interrupted so that a group of cases of *heart-block* due to gumma is now well recognized.

The *aortic insufficiency* due to syphilis depends upon aortitis rather than upon disease of the heart-muscle and will be referred to farther on.

In a recent important paper (1914), A. S. Warthin has reported his findings in the heart in 50 cases of congenital and 150 cases of acquired syphilis. Both parenchymatous and interstitial lesions were observed, though often independently of one another. He describes especially a peculiar form of edema (*myxedema*), vascular and perivascular infiltration, and localized *myxoma-like formations*. The *Treponema pallidum* may be more abundant in the wall of the heart than in the liver, and the organisms may be present in great numbers even in the absence of recognizable histological alterations.

PERICARDIUM.—*Syphilitic pericarditis* and *gumma* involving the pericardium are clinical and pathological rarities.

ARTERIES.—In the secondary and tertiary stages of syphilis, the involvement of the arteries may be responsible for the most important clinical pictures. Any of the arteries may be involved, including the aorta, the large arterial trunks, and the smaller peripheral arteries. In the *aorta*, we have been familiar, since the researches of Doehle, Heller, Chiari and others, with the important *mesaortitis syphilitica productiva*, which involves the aorta ascendens and aorta descendens, and which must be separated sharply from ordinary atherosclerosis of the aorta. The disease has been studied clinically by Huchard and by Gallavardin in France as "*aortite sub-aiguë*," by Sir Clifford Allbutt, by Sir William Osler and by Mitchell Bruce in England as "*syphilitic aortitis*," and in the United States, under the same name, by George Blumer, Thomas McCrae, J. T. Halsey, and Warfield T. Longcope. For a general review of the subject, I would recommend especially the study of Longcope's article (1913).

It is the first five or six centimeters of the aorta that are most in-



volved, a fact that explains the incidence of aortic insufficiency, of aneurysm of the ascending arch, and of partial obstruction of the coronary arteries, which so frequently occur as complications of this disease, but there is diffuse dilatation of the descending thoracic aorta also, whereas in endocarditic aortic insufficiency and in atherosclerosis, the ectasia may be limited rather strictly to the aorta ascendens. (Kraus.) The naked eye appearances in the aorta at autopsy and the microscopic findings are characteristic. The *Treponema pallidum* has been demonstrated in the lesions by several different workers. (Reuter in 1906; Schmorl in 1907; Homer Wright and Richardson in 1909; and others.)

The syphilitic spirochetes are probably deposited in the wall of the aorta during the secondary stage of lues, but it is on the average, about 18 years after infection before the symptoms of aortitis manifest themselves, and even 50 years may elapse before the symptoms appear. This long latency is a striking feature of the disease.

Among the early symptoms may be mentioned: (1) slight dyspnea, (2) precordial oppression or pain, (3) attacks of paroxysmal dyspnea or of angina pectoris and (4) attacks of unexplained weakness. When any of these symptoms are present, a Wassermann test should be made and also a roentgenoscopic examination of the cardio-vascular stripe. Usually there is some hypertrophy of the heart and increased pulsation of the vessels of the neck, though, at the beginning, the heart is not enlarged and the blood pressure is normal. If the Wassermann test be positive, and the aorta be diffusely dilated from its root to the diaphragm on roentgenoscopic view, the diagnosis can be made almost with certainty. It is believed that the paroxysmal dyspnea is due to acute bronchospasm, which in turn may be reflexly caused by irritation of nerves in the root of the aorta by the luetic inflammation.

The relation of *aortic aneurysm* to syphilis was long suspected before the proof of the etiological relation (in the majority of cases) could be brought. Sir William Osler, long an advocate of the luetic origin of aneurysms of early and middle life, has reviewed the evidence in his interesting Schornstein lecture (1909). Aneurysm in later life may be due to atherosclerotic change independent of syphilis, and mycotic aneurysms may occur in early life; but by far the majority of aneurysms of the fourth and fifth decades of life are due to syphilitic aortitis. In nearly all cases the Wassermann reac-

tion is positive, and at autopsy the characteristic luetic lesions are demonstrable in the aorta; in a few instances the *Treponema pallidum* has been stained in the wall of the aneurysm.

The fact that the majority of cases of *aortic insufficiency* developing in adults are the result of syphilitic aortitis was a discovery of later date. A feeling of burning behind the sternum may be an early symptom. Citron (1908) first called attention to the positive Wassermann reaction in the majority of cases of aortic insufficiency and his observation has been manifoldly confirmed and extended since, notably, in this country, by Collins and Sachs (1909), by Paul W. Clough in my clinic (1910), by W. T. Longcope (1910), and by R. M. Pearee (1910). It turns out that the Wassermann reaction is positive in about 75% of all cases of aortic insufficiency; in the other 25%, rheumatism (in early life) and atherosclerosis (in later life) are the commonest causes.

When the aortic insufficiency is due to rheumatism it is usually associated with a mitral lesion.

Attacks of *angina pectoris*, or so-called *stenocardiac attacks*, due to narrowing of the coronary arteries occur in some of the cases of luetic aortitis but by no means in all. In patients under 50, angina pectoris is often due to lues, whereas after 50 atherosclerosis rather than lues is the more common cause. In every case of angina pectoris a Wassermann test should be made.

Attacks of pain in one side of the chest, may, in syphilitic aortitis, be due to *involvement of the orifices of the intercostal arteries*. On the right side, this pain may be confused with referred pain from the pylorus, the gall-bladder, or the capsule of the liver (in perihepatitis).

A *general dilatation of the aorta* may be due either to luetic aortitis or to arteriolar sclerosis with hypertension. (See Thomas McCrae's article and the article by F. Kraus.) To differentiate between them, the rest of the body should be studied, and the Wassermann test should be applied. It is surprising how often an unsuspected dilatation of the aorta is found when routine examinations of the cardio-vascular stripe by roentgenoscopy are made in men and women in middle life. Eisler and Kreuzfuchs on the basis of roentgenoscopic studies describe three types of dilatation in aortic syphilis—the ascendens type, the arcus type, and the descendens

type—in addition to diffuse dilatation of the whole thoracic aorta.

An important practical deduction may be drawn from these studies. It seems probable that the positive Wassermann reaction of latent syphilis is often due to a smouldering process in the aorta. Thorough treatment of these “latent” cases of syphilis will go far toward preventing the terrible arterial complications of lues that are so common 15 or 20 years after infection.

Syphilitic disease of the *larger arterial trunks* other than the aorta is commoner than is supposed. *Occlusion of the larger arteries* was first described by John Davy (brother of Sir Humphrey Davy) in 1839. Snow described the condition in a patient with syphilis and aortic aneurysm as early as 1880. Ziegler, in Germany, and Gurd and Wade (1911), in the United States, have described cases of luetic arteritis involving vessels other than the aorta. A good review of the subject of occlusion of large arteries as a result of syphilitic arteritis will be found in the article by Darling and Clark who had exceptional opportunities of studying the condition among negroes in the Ancon Hospital, Panama. The cerebral symptoms that follow occlusion of the carotid artery have been carefully described by J. R. Hunt (1914).

Syphilis may also involve the *smaller arteries and the arterioles*. A predilection-site is at the base of the brain where a *gummatous arteritis* (with arachnoiditis) is responsible for many of the disturbances of cerebrospinal lues. Since the fundamental studies of Heubner (1874), the importance of luetic arteritis in the cerebrum has been emphasized by many. Good collective reviews will be found in the monographs by F. W. Mott (1910), by H. Oppenheim (1903), by M. Nonne (1909), and by B. Sachs (1915).

The *Treponema pallidum* was demonstrated in luetic arteritis at the base of the brain by Benda in 1906, and by Strasman in 1910. Careful studies of the alterations in arterial structure in syphilis were published by H. M. Turnbull in 1915.

Hemiplegic attacks, hemianesthesias, aphasias, hemianopsias, and other evidences of focal vascular lesion may be met with, clinically, in luetic arteritis of the cerebral vessels. The oscillation of the symptoms, especially at the beginning, is characteristic, as is their combination with symptoms pointing to a syphilitic basilar meningitis (headaches, mental hebetude, eye-muscle paralyses, polyuria,

etc.), and as is the evidence that the lesions that are causing the symptoms must be multiple.

**VEINS.**—There is considerable literature dealing with syphilis of the veins. Thus *phlebitis* and *thrombophlebitis* are not uncommon in the secondary stage of syphilis. When the deep veins of the extremities are involved, a condition like phlegmasia alba dolens may appear. When the superficial veins are diseased, the veins feel thickened, often nodular or moniliform; and there is very little pain and no edema. In one form, in which the cutaneous and subcutaneous veins are affected, the picture may resemble that of erythema nodosum.

**LYMPHATIC SYSTEM.**—The swelling of the regional lymph glands near a Hunterian chancre, and the general lymph gland enlargement of secondary lues are well-known instances of *lymphadenitis syphilitica*. *Gumma* of the lymph glands may occur in tertiary lues. A *lytic lymphangitis* undoubtedly exists, and it may be that some of the cases described as *syphilitic elephantiasis* belong under this heading, but none of these conditions has been studied as carefully clinically or pathologically as is desirable.

#### E. SYPHILIS OF THE DIGESTIVE APPARATUS

**MOUTH CAVITY.**—This may be involved in any one or all three of the stages of syphilis. The primary lesion may occur on the lip, tongue or tonsil, and is associated with indolent swelling of the regional lymph glands. The lip is probably the commonest extragenital site of the Hunterian chancre.

In secondary syphilis, we often see (1) the well-known *syphilitic sore-throat* (*angina syphilitica*), (2) characteristic *mucous patches*, and (3) small syphilitic *ulcers* and *fissures*, especially at the angles of the mouth (*rhagades*), the margins of the tongue, or on the palate.

In tertiary syphilis, *gummata* are common in the musculature of the tongue, in the periosteum of the hard palate, and in the tissues of the velum palatinum. On softening and breaking down, ulcers may appear with irregular borders and yellowish-white, speckled base. As everyone knows, such lesions may be very destructive, sometimes perforating the hard or the soft palate, or, on healing, they may leave large white radiating scars and deformations.

*Smooth atrophy of the base of tongue*, though not always due to lues, is most often the result of a *chronic interstitial glossitis*. It oc-

curs both in congenital lues and in the tertiary stage of acquired lues.

Syphilis of the salivary glands occurs but is rare.

A dystrophy of the teeth, of great importance for the diagnosis of congenital syphilis, is that designated as *Hutchinson's teeth*. The upper medial incisors show crescentic notches. It is asserted that the *Treponema pallidum* has been demonstrated in developing teeth in children dead of congenital lues.

PHARYNX.—The mucous membrane of the pharynx is subject to lesions similar to those that occur in the mucous membrane of the mouth in all three stages of syphilis. Primary lesions are rare, but in the secondary stage a *catarrhal pharyngitis* and *mucous patches* on the pharynx are common. *Gumma* of the pharynx, with ulceration and scarring, is often seen in tertiary lues. Sometimes the soft palate becomes adherent to the posterior wall of the pharynx.

ESOPHAGUS.—This tube is only very exceptionally involved in lues. W. G. Bailey has described a *chancre* of the esophagus acquired through tobacco! A few cases of *gummata* and of *stenosing scars* have been reported (Choso; Mracek; Newmann).

STOMACH.—In CONGENITAL LUES, pathologists have described small-celled *infiltrations* of the wall of the stomach, and, more rarely, *gummata*. In ACQUIRED LUES, *gummatous infiltrations* and *ulcers* occasionally occur though they are rare. It is interesting that many of the reports have come from American and Canadian observers. Thus Hemmeter and Stokes have described a *chronic hypertrophic gastritis* of syphilitic origin, and S. Flexner has reported the *perforation of a syphilitic gastric ulcer*. The general subject of gastric syphilis has been discussed by Bird, Chase, Curtis, Einhorn, Hoover, Kohn, W. G. Morgan and others in the United States.

INTESTINES.—Syphilis of the intestines is also rare. By far the most important form is the *chronic gummatous proctitis* that leads to chronic *ulceration* and *stricture* of the rectum. It occurs chiefly in female prostitutes. A similar condition can follow gonococcal proctitis.

PANCREAS.—In CONGENITAL LUES, an *interstitial pancreatitis* occurs that prevents the development of the secreting parenchyma, though the islands of Langerhans are preserved. The condition has been studied in the United States by A. P. Condon (1899-1901) and by R. M. Pearce (1904).

In ACQUIRED LUES, a *chronic indurative pancreatitis* has also been described, usually in association with *gummata* of the pancreas. (Schlagenhauser.)

LIVER.—Of all the viscera, the liver is the organ most often, and most conspicuously, attacked by the virus of syphilis.

In CONGENITAL LUES, a *hepatitis interstitialis chronica diffusa* is the common lesion, though *gummata of the liver* may be present with, or without, this diffuse interstitial change. *Gummata* most often occur, according to pathologists, in the form of miliary nodules; larger syphilomata may also occur but are less common in congenital than in acquired lues.

In ACQUIRED LUES, a *hepatitis interstitialis chronica disseminata* is often met with. It leads to the coarsely scarred liver known at autopsy as *hepar lobatum*, large areas of relatively healthy liver tissue being separated from one another by deep sulci. *Gummata of the liver* are also common in acquired syphilis. They may be single or multiple. Gummatus infiltrations may also, on healing, leave a multilobular cirrhosis behind. *Amyloid change* in the liver is frequently associated with lues hepatitis.

Clinically, a nodular liver due to lues may be confused with carcinoma hepatitis. In every doubtful case a Wassermann test should be made and antiluetic therapy tried. At an autopsy made recently by Dr. M. C. Winternitz on the body of a patient whom I had seen in consultation, *gummata* were present in a liver that contained also a primary cancerous growth.

In secondary and tertiary syphilis, *enlargement of the liver with fever and jaundice* may be due to an interstitial hepatitis. It is probable that many of the cases of fever of obscure origin in syphilis are due to hepatitis.

SPLEEN.—In secondary syphilis, a *splenomegaly with lymphocytosis*, and, sometimes, with jaundice, has been repeatedly observed.

In tertiary syphilis, the spleen, like the other viscera, is subject to two main types of involvement: (1) *splenitis chronica interstitialis* and (2) *splenitis gummosa*. Both these forms are met with in lues congenita as well as in lues acquisita.

#### F. SYPHILIS OF THE UROPOIETIC APPARATUS

KIDNEYS.—In CONGENITAL LUES, though, at autopsy, the *Treponema pallidum* has been demonstrated in the interstitial tissue and between

the epithelial cells lining the uriniferous tubules, no specific alterations in renal structure have been found.

In ACQUIRED LUES, clinicians have described a *syphilitic nephritis*, but pathologists are in doubt as to its existence, though they recognize a multiple scarring of the kidney in syphilitics (*nephritis interstitialis chronica fibrosa multiplex*) that may be a sequel to a true disseminated interstitial luetic nephritis. Certainly, too, some *amyloid kidneys* are to be regarded as a sequel of lues.

The French internists have written a good deal about the *Mal de Bright syphilitique précoce*, or *Syphilis rénal précoce*, and in this country, Lafleur (1896), Fordyce (1897) and Montgomery (1901) have reported cases. Careful chemical studies of the condition have been made by Salkowski of Berlin (1902).

*Gummata* of the kidney have been reported by Bowlby (1896-7) and by Erdheim (1902).

URETERS.—Very little has been written on syphilis of the ureters. Apparently the involvement of these tubes in the disease is rare. See the article by J. K. Prokseh (1899).

URINARY BLADDER.—Aside from the *gummata* that have occasionally been observed in the region of the trigonum vesicae, very few cases of vesical syphilis have been reported. Of the recent articles, I would refer to that of Mikhailoff (1911) and that of Picot (1912).

#### G. SYPHILIS OF THE MALE GENITAL ORGANS

TESTICLES, EPIDIDYMIS, AND DUCTUS DEFERENS.—In CONGENITAL LUES, involvement of the testis is exceedingly rare. On the other hand, in ACQUIRED LUES, a localization in the testicle is a common phenomenon, either in the form of an *orchitis fibrosa diffusa*, or in the form of *gummata*.

In *diffuse syphilitic fibrous orchitis*, there is chronic inflammatory change in the interstitial tissue of the testicle; it leads to compression and atrophy of the seminiferous tubules and, finally, to induration and diminution in the size of the gonads. Other forms of fibrosis testis (after mumps, tuberculosis, leprosy, gonorrhea, trauma, etc.) may be hard to rule out, especially in the end stages.

In tertiary lues, *gummata of the testis* may occur singly or multiply, varying in size from that of a pea to that of a hickory-nut. These *gummata* are usually firm and somewhat elastic nodules. As a rule there is no spontaneous pain, and only slight sensitiveness on

pressure. If a gumma break down and give rise to a fistula, it can usually be distinguished from a fistula of tuberculous origin, first, by the predominant involvement of the testis rather than the epididymis in the process, and secondly, by Reclus's sign; namely, that luetic fistulae are usually situated anteriorly whereas tuberculous fistulae are generally situated posteriorly (except in the rare cases of *inversio testis*).

Neoplasm of the testis may be mistaken for gumma. We should be on the look-out for tumor-metastases, even in patients who have a positive Wassermann reaction, especially if antiluetic therapy has no effect in two or three weeks.

It is true that a *syphilitic epididymitis* does sometimes occur in secondary lues. It is usually painless. The history of the patient may give the clue to diagnosis.

SEMINAL VESICLES.—Syphilis of these sacs is rare, though tuberculous and gonorrhoeal involvement are common. P. Cohn has reported a case of *hemorrhagic syphilitic disease of the seminal vesicles* (1907).

SPERMATIC CORD.—*Gummata* of the spermatic cord have been described by R. F. Campbell (1901), by H. Goldenberg (1901) and others. The condition is rare.

PROSTATE.—Relatively little has been written upon syphilis of this organ, whereas, as is well known, tuberculosis of the prostate is a common affection. For a summary of what is known on the subject, the article by Rochon (1897) may be consulted. Russian and Polish observers have also reported on cases of *gummata* of the prostate.

PENIS, MALE URETHRA, AND SCROTUM.—Here the common lesion is the initial or Hunterian *chancre*. Since this belongs to external syphilis it will not be considered in the present review.

## II. SYPHILIS OF THE FEMALE GENITAL ORGANS

OVARIES.—Very little is known of syphilis of the ovaries and Fallopian tubes. French writers have described a *sclerosis* of the ovaries of syphilitic origin, associated with a rebellious form of *metrorrhagia*, that yields to antiluetic treatment. If, however, we are to judge from the reports of pathologists on ovarian lues, we must conclude that the condition is rarely met with at autopsy.

UTERUS.—Aside from *chancre of the cervix* and occasional gum-



*mata* in the wall of the uterus, but little is known regarding syphilis of this organ.

VAGINA.—The *initial lesion* may sometimes be observed on the vaginal wall, and the diagnosis made by demonstrating the presence of *Treponema pallidum* in juice obtained by scraping. In secondary lues, an *erythematous vaginitis* has been described. Ulcerating *gummata* of the vagina and vulva have been repeatedly observed in tertiary syphilis.

#### I. SYPHILIS OF THE BONES, MUSCLES, AND JOINTS

BONES.—In CONGENITAL LUES, one of the most important lesions met with is the *osteochondritis syphilitica* of Wegner. It is present in nearly every case of congenital lues. The disease involves the junction of the epiphysis with the diaphysis in the long tubular bones, and the junction of the cartilage with the bone in the ribs. It is responsible for the separation of the epiphyses so often met with in congenital lues, as a result of slight trauma either after birth or *in utero*. The most frequent site, perhaps, of separation of the epiphysis is the lower end of the radius, though other common sites are the lower end of the femur, the bones of the leg, and the lower end of the humerus. The well-known *dactylitis syphilitica* of congenital lues belongs here.

Two other forms of bone-disease are met with in congenital syphilis; namely, *periostitis ossificans*, and *periostitis gummosa*. In the former there are osteophytic deposits on the ends of the diaphysis of the long bones, and these often extend along the shaft to its middle; sometimes several layers of alternating compact and spongy bone are laid down beneath the periosteum. In the latter, multiple small periosteal gummata (syphilomata) appear in the periosteum, most often on the bones of the skull, not infrequently in association with the osteochondritis syphilitica referred to above.

The roentgenographic findings in these several conditions are characteristic.

In ACQUIRED LUES, the changes in the bones have long been observed and carefully studied. In the secondary stage, there may be temporary areas of periostitic swelling causing "rheumatic" or "neuralgic" spontaneous pains, or circumscribed tenderness. At night, the pains may be especially severe (*dolores osteocopi*).

In tertiary syphilis, two forms of syphilis of the bones occur: (1)

*gummatous periostitis and osteomyelitis*, and (2) *ossifying periostitis and ostitis*. In the former, central gummata may weaken the bones and lead to spontaneous fractures, whereas peripheral gummata (beneath the periosteum) give rise to the well-known *syphilitic nodes* on the superficial bones (calvarium, sternum, clavicle, tibia, ribs). The so-called *spondylitis syphilitica* that affects by preference the cervical spine is in reality a gummatous osteitis of the bodies of the vertebrae. Saddle-nose, perforation of the nasal septum, and perforation of the hard palate are due less to a process beginning in the bone than to the extension of a process from the ulcerated mucosa (M. B. Schmidt).

In ossifying periostitis and ostitis, *diffuse hyperostoses* develop, especially on the calvarium and the tibia. *Osteosclerotic changes* occur in the bone.

Clinically, we have to differentiate syphilis of the bones from tuberculosis, sporotrichosis, chronic staphylococcic osteomyelitis, and sarcoma and other neoplasms.

MUSCLES.—Two forms of syphilis of the muscles have been described: (1) *myositis syphilitica gummosa*, the most common luetic disease of muscular tissue; and (2) *myositis syphilitica fibrosa diffusa*, occasionally met with, especially in the M. biceps and the M. masseter.

Lues of muscle has been studied in the United States by J. B. Herrick (1896) and by J. A. Fordyce (1903). Among the papers by foreign physicians, those of Byrom Bramwell and of O. Busse may be consulted.

The muscles may be involved either in congenital or acquired lues.

JOINTS.—Joint syphilis may occur either in the congenital or the acquired disease. It is, however, a relatively rare affection.

In secondary lues, slight joint effusions may accompany the florid stage, and complaints of so-called "rheumatic pains" in the joints are common.

In tertiary lues, the knee joint is most often attacked though occasionally other joints including those of the spine may be concerned. Monarticular is commoner than polyarticular involvement. The disease may start either in the synovial membrane or in the ends of the bones entering into the formation of the joint. Both *gummatous* and *diffuse fibrous inflammations* are met with. See the article by J. Hutchinson, Jr., and that by A. O'Reilly.

The "Charcot joint" of tabes is not due to direct involvement of the joint by syphilitic inflammation. It is probably a traumatic arthritis occurring in a joint made anesthetic as the result of the tabetic involvement of the posterior roots of the spinal nerves.

#### J. SYPHILIS OF THE NERVOUS SYSTEM

In CONGENITAL SYPHILIS, the nervous system may be the site of a *gummatous meningitis*, often with the involvement of the underlying brain or spinal cord (*meningo-encephalitis*; *meningo-myelitis*). *Miliary gummata upon the ependyma* of the lateral ventricles have been observed. Involvement of the arteries by a luetic meningitis, or the occurrence of a *gummatous arteritis* may lead to encephalomalacia or to myelomalacia with corresponding focal symptoms.

In how far *epilepsy*, *idiocy*, and *imbecility* are related to congenital lues has been much discussed. That syphilis plays an etiological role in at least some of the cases there can be no doubt. As to the relations of lues to *congenital anomalies* (hypoplasia; asymmetry; absence of parts of the nervous system), we still lack definite knowledge.

In ACQUIRED SYPHILIS, involvement of the central nervous system is very common; indeed, it is the greatest danger that menaces persons infected with the *Treponema pallidum*. The nervous system may be invaded in the secondary stage, but more often it is in the tertiary stage that nervous symptoms appear (*lues cerebrospinalis*). Many years after a luetic infection, tabes dorsalis or dementia paralytica may develop (*parasyphilis*).

BRAIN.—Here the two main forms of luetic disease are: (1) a *gummatous arteritis* affecting the A. cerebri media (hemiplegia; aphasia), the A. cerebri posterior (hemianesthesia; hemianopsia), the A. vertebralis (unilateral bulbar paralysis), or the A. basilaris (focal symptoms pointing to medulla oblongata or pons); and (2) a *gummatous meningitis or meningo-encephalitis*, that may involve any part of the meninges, though the base of the brain in the middle fossa of the skull is by far the commonest site. Headache and signs of increased intracranial pressure are often present. The cerebral nerves at the base of the brain are often involved causing characteristic symptoms (eye-muscle paralyses; symptoms referable to injury of optic tracts or chiasm; anosmia; facial neuralgia or facial palsy; deafness; anarthria; atrophy of tongue, etc.). When the meninges of the

convexity of the brain are invaded, symptoms of focal cortical irritation or destruction may appear (monoplegia; Jacksonian epilepsy).

Rarely, a third form of luetic involvement of the brain is encountered; namely, *isolated gumma in the brain substance*. The symptoms are like those of neoplasm in the same situation.

SPINAL CORD.—Here, too, syphilis is met with in two main forms: (1) *gummatous arteritis of the spinal arteries* causing myelomalacia with signs of complete or incomplete transverse lesions of the spinal cord, and (2) *gummatous meningo-myelitis* involving the anterior and posterior roots of the spinal nerves as well as the spinal cord itself and giving rise to corresponding symptoms (neuralgias; paresthesias; root-pains; muscular atrophies; paraplegias, etc.).

The coming and going of the symptoms ("oscillation") is a characteristic feature of cerebrospinal lues. There are often periods of marked regression of the symptoms, though recurrences are common, often with changes in distribution of the symptoms. Eye-muscle paralyses and hemiplegia in young people who have neither a cardiopathy nor a nephropathy should make one think of syphilis of the nervous system. In every patient who presents signs of syphilis elsewhere in the body (skin; aorta), the nervous functions should be carefully examined and if disturbances are found the cerebrospinal fluid should be studied (as well as the blood serum). The differential diagnosis of cerebrospinal lues is not without its difficulties, though, if modern technic be fully applied, the clinician will rarely be left in doubt. Among the maladies likely to be confused with it I may mention (1) cerebral atherosclerosis, (2) tumor cerebri (3) multiple sclerosis and (4) the functional neuroses.

In the spinal cord (5) *simple myelitis* or (6) *compression myelitis* may resemble meningo-spinal lues.

PARASYPHILIS.—We know now that Erb was right in his belief that the so-called parasyphilitic diseases, including tabes dorsalis and dementia paralytica, are due to the virus of syphilis. In 1913, Noguchi and Moore demonstrated the presence of the *Treponema pallidum* in the brain in cases of general paresis, and their work has since been confirmed by a number of observers.

Just how the virus of syphilis acts in these parasyphilitic diseases has been much disputed. In *tabes dorsalis*, some lean to a primary toxic degeneration of the nerve fibers, others to a degeneration

secondary to neuritis of the posterior roots, to compression of the roots by "syphilosis" of the meninges, or to a syphilitic lymphangitis in the domain of the posterior funiculi of the spinal cord. In *dementia paralytica*, the lesions are those of a meningo-encephalitis of peculiar type, associated with extensive atrophic and degenerative changes in the brain substance, especially in the cortex of the frontal lobe and of the island of Reil of each hemisphere.

Careful somatic and psychiatric examinations make the diagnosis of tabes and of dementia paralytica easy, especially if the findings in the nervous system and in the cerebrospinal fluid are adequately made and valued.

On certain other nervous diseases that have been attributed to syphilis (e.g., Erb's syphilitic spinal paralysis) I shall make no comment since their exact nature and their precise relations to lues (if any exist) have yet to be worked out.

#### K. SYPHILIS AND THE ENDOCRINE GLANDS

During the past few years, since clinical interest in diseases of the ductless glands has so greatly deepened, some attention has been paid to the relation of syphilis to the endocrinopathies.

**HYPOPHYSIS CEREBRI.**—In Cushing's admirable monograph on *The Pituitary Body and Its Disorders* (p. 263), a description is given of a man of 32 who suffered from headaches, glycosuria and polyuria and who died with symptoms suggestive of intracranial growth (projectile vomiting; disturbances of consciousness and speech). At autopsy, the brain was removed and, on examination, besides a chronic leptomeningitis, Cushing found a syphiloma large enough to be distinctly visible to the naked eye on section, and involving the anterior and intermediate lobes of the pituitary body. Syphilis had not been suspected. It would be a good rule in every case of diabetes insipidus and of diabetes mellitus to think of syphilis and to have a Wassermann test made. I personally had the chagrin two years ago to miss the diagnosis of syphilis in an important case. The patient had diabetes mellitus and some atherosclerosis. He showed some mental confusion and signs of aphasia that were attributed to an atherosclerosis of the cerebral arteries. It had been matter of routine in the private wards to make a Wassermann test in every patient and it was customary to have my attention always called to cases in which the reaction was positive.

In the man mentioned, by some oversight, the test was not made, and I had assumed that it had been made and had been found negative. Improvement occurred but was not satisfactory. A few months later, my friend, Dr. J. F. Mitchell, of Washington, had a Wassermann test made, found it positive, gave antiluetic therapy and had the satisfaction of obtaining quickly a remarkable improvement in all the symptoms!

Very little has been written upon lues of the hypophysis cerebri but I feel sure that a systematic study of the relations of this gland to lues would in time prove to be rewarding. (See Fitcher's article in 1902 on the relations of diabetes insipidus to syphilis.)

**THYROID GLAND.**—An excellent review of syphilis of the thyroid gland and of the bibliography bearing upon it will be found in the article by B. F. Davis, of Chicago (1910). About twenty cases of *gumma* of the thyroid have been described. The lesion seems to be very rare. The gummata may be small or large and may or may not produce symptoms. Sometimes signs of myxedema, sometimes those of Graves's disease accompany the lesion. The disease may affect the thyroid directly, or it may extend into it from a syphilitic perichondritis of the larynx.

**PARATHYROID GLANDS.**—I have not been able to find references to syphilitic involvement of the parathyroid glands, though tuberculosis of the glands has been observed in one case of tetany.

**THYMUS.**—A full review of the bibliography of syphilis of the thymus will be found in Wiesel's article (1912). Three forms of syphilitic disease occur, chiefly in lues congenita. They are: (1) *chronic interstitial thymitis*, (2) *gummata of the thymus*, and (3) the so-called *Dubois' abscess*, which Chiari holds to be a cavity lined by epithelium and derived from accumulation of cells within a Hassal's corpuscle, whereas Simmonds, and Schlesinger ascribe the cyst formation to arrest of development of some of the epithelial tubules that give rise to the thymus.

It would appear that luetic disease of the thymus may, rarely, be the cause of thymus-death in infancy.

**PANCREAS.**—See Syphilis of the Digestive Apparatus.

**SUPRARENALS.**—These bodies may be diseased either in congenital or in acquired lues. Here, too, at least two forms of syphilitic process are encountered: (1) a *sclerosis* due to chronic interstitial luetic inflammation and (2) *gummata*. The *Treponema pallidum*

has been demonstrated in the suprarenal by Jacquet and S  zary.

GONADS.—See Diseases of the Male and Female Genital Organs. It is believed that some cases of *eunuchoidismus* may be due to luetic disease injuring the endocrine function of the gonads.

#### CONCLUSION

The above brief survey reveals how widespread the manifestations of syphilis in the human body may be; and it shows clearly that the recognition of syphilitic lesions at all their possible sites, and in their several forms, presupposes not only a knowledge of the spirillodiagnostic and immunodiagnostic methods of examination for the luetic virus and for the substances that appear in the blood and in the cerebrospinal fluid in luetic infections, but, in addition, a thorough acquaintance with the diagnostic methods of internal medicine as a whole, inclusive of all the medical specialties.

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## SYPHILIS OF THE THYROID

(With the Report of a Probable Case.)

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**S**YPHILIS of the thyroid undoubtedly is a rare condition. Neither Keyes,<sup>1</sup> Ravogli,<sup>2</sup> nor Lambkin,<sup>3</sup> mention it in their text books on syphilis, while Marshall<sup>4</sup> contributes the following short paragraph on the subject: "Mauriac described swelling of the thyroid gland in secondary syphilis. According to Gougerot, three cases with symptoms of exophthalmic goiter which were improved by anti-syphilitic treatment have been reported by Penzold. The same author also states in rare cases, fibrogummatous or gummatous changes may occur with symptoms of myxedema."

Delafield and Prudden,<sup>5</sup> writing of the thyroid in their text book on Pathology, state that, "syphilitic inflammation, with the formation of gummata, has been described, but is rare."

Adami<sup>6</sup> dismisses the subject by stating that the condition is rare; that eleven undoubted cases are found in the literature, while MacCallum,<sup>7</sup> in his excellent new work on Pathology, ignores syphilis of this gland.

It was Montgomery<sup>8</sup> who suggested that the comparative infrequency of paresis and tabes in women might be due to the greater activity of the thyroid in this sex on the theory that iodothyryn, the principle constituent of thyroid secretion, exerted specific influence on the *Treponemata pallida* and so modified them as to prevent neural syphilis.

It may be possible that the rarity of syphilis of the thyroid is due to the presence of iodothyryn in this gland which in the majority of cases prevents the development of the *Treponemata* in this location.

Although it is rare, syphilis affects the thyroid both as an early and as a late manifestation. Mauriac<sup>9</sup> stated that tumefaction of the thyroid was common in early syphilis, and quoted a case which he described as syphilitic goiter in which the gland became so large

that it compressed the trachea and larynx, causing hoarseness and difficulty of respiration.

Angel-Reimers<sup>10</sup> observed enlargement of the thyroid 86 times in 152 female patients and 44 times in 98 male patients, which was confined to the lateral lobes, not involving the isthmus. The swelling was soft, painless, and would not have been observed if it had not been searched for. He states that it appears during the secondary incubation period or with the first constitutional symptoms, is uninfluenced by treatment, but disappears gradually in a year or two as does the swelling of the lymphatic glands.

Lockwood<sup>11</sup> in 1895 reported five cases of early involvement of the thyroid and strangely enough all of these cases occurred in women. Their ages varied from 16 to 23 years and all occurred during the so-called secondary stage of the disease. All were accompanied by general lymphatic enlargement and a roscolar syphiloderm.

Syphilitic involvement of the thyroid later in the course of the disease, while possibly not so frequent as the early involvement, has been more frequently reported, and the cases are probably more authentic. One of the earliest records of such involvement is that of Demme,<sup>12</sup> who in 1879 reported three congenitally syphilitic children in whom gummatous nodules were observed in the thyroid. These gummata were described as grayish-red or grayish-yellow nodules resembling gummata of the liver microscopically.

Gombault<sup>13</sup> in 1884 published a case of tumor of the thyroid occurring in a patient diagnosed as suffering from congenital syphilis. This diagnosis was based upon the presence of an interstitial keratitis and tibial periostosis. Histologically the tumor was seen to consist of a caseous center surrounded by a thick wall of connective tissue containing many embryonic connective tissue cells and a few giant cells. Obliterating arteritis was also observed. As no tubercles were found and the tubercle bacillus could not be demonstrated, a diagnosis of syphilis was made which was concurred in by Cornil.

Fraenkel,<sup>14</sup> in 1887, reported a case which he considered gumma of the isthmus of the thyroid. This occurred in a woman of 41 who died of syphilis. She had ulcerating gummata of the trachea and bronchi; and, postmortem, gummata of the liver and kidney were found, as well as thickening of the frontal bone and tibia. A rather hard yellowish-gray mass 2.5 cm. x 2 cm. x 1 cm. was found at the point where the isthmus joined the right lobe of the thyroid. Micro-

scopically there was an infiltration of round cells, but no giant cells were observed. While there was but little evidence of necrosis, the Lustgarten bacillus was demonstrated which was considered by Fraenkel as characteristic of syphilis.

Garnier,<sup>15</sup> in 1889, studied in his thesis the thyroid alterations in five still-born congenital syphilitics and established in four of them interstitial and parenchymatous lesions.

Lancereaux<sup>16</sup> noted at the autopsy of so-called tertiary syphilitics that the thyroid gland appeared paler, smaller and firmer than normal, and histologically that there were large bands of fibrous tissue pressing upon the vesicles.

Kohler<sup>17</sup> observed a case of myxedema in a woman of 48 in which there was a hard nodular tumor-like mass above the manubrium which disappeared under iodide therapy, the myxedema also disappearing.

Pospelow<sup>18</sup> reported a case of myxedema occurring in an undoubted syphilitic in which the thyroid was slightly enlarged and hardened. This case was also cured by antisiphilitic treatment.

Clarke<sup>19</sup> reported a case in 1897 of a woman 38 years of age who had been treated four years previously for gumma of the right arm. No other history of syphilis could be obtained. About two weeks before being examined she found difficulty in swallowing and breathing and her voice became husky. Occasional attacks of dyspnea occurred which caused great distress. A hard cylindrical mass extending from the thyroid bone to the manubrium was observed in the mid-line of the neck anteriorly. The upper part of this showed a typical gummatous ulcer. A few days later breathing became so difficult that laryngo-tracheotomy was performed and a tube inserted, which was followed by immediate relief. Microscopical examination of the growth showed a typical gumma, but no thyroid tissue. The swelling rapidly disappeared under potassium iodide.

Mendel<sup>20</sup> in 1906 published a rather complete study of syphilis of the thyroid. In this paper he refers to two cases described by Cuttner in 1898. The first of these was a woman of 39, who at the age of 18 had had an exanthema and two years later gave birth to a still-born child. On examination the thyroid was found to be enlarged and very hard. Believing it was malignant, it was removed, but microscopical examination revealed the fact that it was a gumma.

In the second case, a man 27 years of age presented similar symp-

toms to those observed in the preceding case. By microscopical examination of a small piece of the tumor, it was found to consist of sclerotic connective tissue, round cell infiltration and characteristic proliferative changes in the blood vessels. It also disappeared in three weeks under large doses of iodine.

Of the three other cases described by Mendel the first was that of a woman of 38, who at the age of 12 had noticed a swelling in the neck, which during the six months previous to the examination had become the size of a child's head. It was situated on the right side and was hard and nodular. While there was no pain there was great dyspnea and tracheotomy was performed. The growth was extirpated two days later and the patient died of heart failure on the second day following. At autopsy an amyloid spleen and gummata of the liver were observed. The tumor of the thyroid, which measured 11 cm. x 10 cm. x 9 cm. and included the entire right lobe, was hard, firm, and dry, varying in color from a pale red to an orange yellow. On section, radiating strands of connective tissue extending from the periphery inward were observed, and localized areas of thyroid tissue were seen near the periphery, while the center consisted of a structureless mass. In the intermediate zone there were spindle-shaped and Langhans' giant-cells. These latter cells caused Mendel to consider the condition as tubercular, but the inability to demonstrate tubercle bacilli, the small amount of necrosis, and the typical syphilitic arteritis of the blood vessels of the outer two coats made the diagnosis of *struma syphilitica* certain.

The next case of Mendel's was also a woman of 38 years of age. She was in good health and had two healthy children, although in the left lobe of the thyroid there was a hard nodular lump the size of a hen's egg. The right lobe of the thyroid was also somewhat enlarged but this condition had existed for years while the tumor of the left lobe had developed in three months. Under potassium iodide this disappeared and never returned.

The final case of Mendel's was a woman 63 years old in whom a hard tumor developed in the left lobe of the thyroid, which was already somewhat enlarged. This grew rapidly and in about five months there was such great difficulty in swallowing and breathing that tracheotomy was performed. The esophagus was also very much involved and the condition was diagnosed as incurable cancer. Three months later when she was seen by Mendel the neck

measured 45 cm. in circumference and contained a tumor which reached from one angle of the jaw to the other. It was hard but caused no pain. However, the patient suffered with severe attacks of dyspnea and heart weakness. While the glands of the neck were slightly swollen, they were not of the consistency of cancerous glands, and as there was no ulceration either inside or out and no metastasis, combined mercury and potassium therapy was begun. In three weeks the circumference of the neck had diminished from 45 cm. to 23 cm. The cannula was removed from the trachea, the wound healed and in a short time she was pronounced cured. However, six weeks later a hard painful tumor developed in the left lobe of the thyroid, which increased in size rapidly causing great pain and soon involved the left brachial plexus and practically all the structures of the neck, death occurring in six weeks. Mendel considers this latter case as one which originally was syphilitic, but followed by malignant change.

D'Arcy Power<sup>21</sup> reported the case of a waiter, age 53, who complained of a lump in his neck which he had first noticed one month previously. This patient had contracted syphilis about thirty years before and had received treatment for six months. Since that time he had showed various so-called tertiary lesions which had been cured by potassium iodide. This tumor on the right side of the neck was found to measure two inches by one inch, the long axis pointing obliquely outwards and upwards. It was hard and solid, with a smooth surface and a rounded margin. It was painless, did not pulsate, and was not attached either to the skin or the sternomastoid muscle. The outer end of the tumor was so hard it was thought to be calcified and a radiograph showed a distinct shadow in the position of the swelling.

Under potassium iodide and ammonium carbonate the swelling subsided to half of its original size in two weeks, while in a month it could no longer be felt.

A specimen which is considered as gummatous inflammation of the thyroid is found in the Museum of the Royal College of Surgeons of England (No. 2906-G), and is described in the catalogue as follows.<sup>22</sup> "Base of the tongue, larynx, and thyroid gland, showing gummatous infiltration of the thyroid. The sternothyroid muscle is matted to the left lobe of the thyroid, which on section has a white fibrous appearance towards the periphery, while the

center more nearly resembles normal thyroid tissue. The upper end of the trachea is distinctly stenosed, and it, as well as the base of the tongue, shows the effects of past ulceration. Microscopic sections showed a fibrous tissue richly studded with nuclei. From a woman, about 60, who was brought into Guy's Hospital dead. There were gummata in the liver."

Davis<sup>23</sup> in 1910 reviewed the literature and reported a personal case. This patient, a man, whose age is not given, who gave a history of syphilis five years ago was admitted to Cook County Hospital January 10, 1909, complaining of hoarseness, great inspiratory dyspnea and pain on swallowing, which symptoms had developed four months previously. This condition was constant and exacerbations occurred frequently in which dyspnea was so great that cyanosis was very marked. The neck was somewhat tender in the region of the thyroid cartilage but otherwise negative. On January 18, 1909, tracheotomy was performed with the insertion of a tube under local anesthesia. This did not give relief and the patient died twelve hours later.

At autopsy the following lesions were found: Recent tracheotomy wounds; blood in trachea and bronchi; gummatus perichondritis of the right thyroid cartilage, with partial stenosis of larynx; edema of the arytenoepiglottic fold; enlargement of the cervical lymph glands; gumma of the dura mater with old intracranial hemorrhage and compression of the right parietal and occipital lobes; chronic healing tuberculosis of the apices of both lungs; gummatus infiltration of the right lobe of the thyroid and operative injury of the isthmus of the thyroid; left adhesive pleuritis; radiating atrophic scars in the skin of the forehead and penis.

There were no gross changes in the epiglottis, although the epiglottic folds were swollen, especially the left, which was edematous and gelatinous in appearance. The orifice of the larynx was slit-like and the vocal cords did not open as easily as normal. Almost the entire ventricular space was filled with the edematous mucous membrane of the ventricles of the larynx. The right side of the thyroid cartilage and adjacent tissues were about four centimeters thick, due to a connective tissue induration. This thickening also included a solid tumor-like mass 2 cm. thick on the outer side of the cartilage, which was composed of translucent but firm fibrous tissue. The right vocal cord could not be pushed away from the me-

dian line on account of a thickening in the inner side of the thyroid cartilage similar to that on the outer side. There was thickening of tissue at the site of the right lobe of the thyroid gland. The gland was uniformly and diffusely enlarged, weighing 60 grams. The posterior capsule was dense and translucent on the right side. The upper end of the right lobe was entirely replaced by diffuse, homogeneous fibrous tissue, continuous with the perichondrial thickening. A few small, white nodules were found deeper in the right lobe of the gland, while the left lobe was normal except slightly enlarged.

Further examination showed that the right lobe of the thyroid was 7 cm. long x 5 cm. wide x 2.5 cm. thick with a fairly smooth surface. On section an area 1.5 cm. to 2 cm. in diameter was found in the posterior medial portion of the upper pole of the gland which presented an outer clear, homogeneous semitransparent zone 3 mm. to 5 mm. in thickness and a central opaque, whitish area 7 mm. to 10 mm. in diameter. The outer zone was continuous with connective tissue septa which ran throughout the gland dividing it into irregularly sized oval lobules. Another area of hyaline-like material, 5 mm. to 7 mm. in diameter was found about 1 cm. from the inferior extremity of the gland. This area was also continuous with heavy strands of connective tissue radiating into the gland. These strands and those of the upper pole, converged at a thick walled blood vessel 1.5 mm. in cross-section about the middle of the anterior surface of the thyroid and formed a third area of clear, homogeneous connective tissue.

On the medial side of the right lobe the tissue described in the posterior medial portion of the upper pole extended clear to the surface and was apparently in very close apposition, if not directly continuous, with the perichondrial thickening of the thyroid and cricoid cartilages.

The left lobe of the thyroid gland was 7 cm. long by 3.5 cm. wide by 3 cm. thick and was normal except for a nodule 5 mm. in diameter located 1 cm. from the tip of the inferior pole, which had the appearance of colloid, and more anteriorly a small spicule of whitish material of the consistency of cartilage.

Microscopically the left lobe was found to be poor in colloid but otherwise normal. The right lobe showed a general increase in the perifollicular connective tissue as well as a considerable area in

which no thyroid cells could be demonstrated. The latter area was, as a rule, sharply marked off from the gland cells, but in places there was no line of demarkation, the two types of tissue merging into each other. Thickened strands of perifollicular tissue were continuous with this new growth. The latter was divided into two zones, an outer and an inner. The former, which bordered on, and sometimes infiltrated, the thyroid tissue, was roughly semicircular in shape, fairly thick and to a considerable extent was made up of large spindle-shaped cells lying in a myxomatous matrix. A few small groups of lymphoid cells and a very few large stellate and epithelioid cells were found. Several small giant cells, with three or four nuclei, and a few Langhans' giant-cells were observed. The inner zone was made up of necrotic material with very few large spindle, stellate and endothelial cells. In a few places there were localized areas of connective tissue proliferation made up of a central portion of epithelioid cells and a peripheral portion of lymphoid cells. Sometimes these areas, which were small, were made up entirely of round cells, and sometimes they possessed a necrotic center. In the right lobe of the thyroid there was also present a marked arteriosclerosis with calcification which was not observed in the left lobe. The new tissue growth was quite vascular, the vessels showing a marked proliferation and thickening of the walls, even sometimes total occlusion.

The chief effect on the thyroid tissue was that of pressure as the proliferating tissue confined itself to the interfollicular regions.

The diagnosis of gumma of the thyroid was made which was probably primary in the perichondrium of the cartilages of the larynx and later invading the right lobe of the thyroid by direct contiguity.

Poncet and Leriche,<sup>24</sup> in 1912, reported the clinical findings of a case of syphilis of the thyroid, the histological report of which was made by Favre and Savy in 1913. This case was a woman aged 38, who in 1907 had a tumefaction of the superior extremity of the tibia and the following year an analogous lesion of the sternum, both of which disappeared under iodide therapy. In 1910 symptoms of thyroidism appeared and in 1911 she was placed in the hospital where injections of mercury ameliorated the symptoms which, however, returned. Radiotherapy and a partial thyroidectomy were almost without effect. However one treatment by arsenobenzol caused all of the symptoms to disappear.



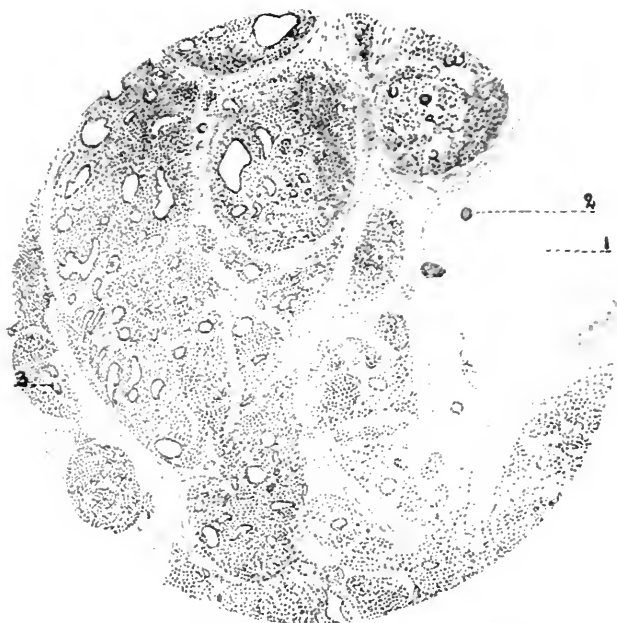


Fig. 1.—Diffuse inflammatory infiltration between the thyroid vesicles which are in progress of degeneration; (1) Gomma with a giant cell (2) at its periphery; (3) Nodular masses enclosing giant cells. (Favre and Savy.)



Fig. 2.—Higher magnification of Fig. 1: (1) Nodular mass with epithelial cells in the center and giant cells; (2) An intra-vesicular pseudo-giant cell. (Favre and Savy.)



The histologic picture was characterized essentially by inflammatory alterations of the interstitial tissue, which was infiltrated with small round cells; by modifications of the thyroid vesicles; by the appearance of so-called specific elements; epithelioid nodules, gummatous formations and giant cells.

Favre and Savy point out that the microscopical picture of syphilis of the thyroid is the same as tuberculosis of this organ, and state that it is possible that a certain number of cases which have been regarded as tuberculosis were in reality syphilis. These authors state that examination for the bacillus of Koch is often negative in tuberculosis of the thyroid and examination for *Treponemata* in syphilis of the thyroid is also often negative, as was the result in their case. They further state that the other laboratory evidence, the clinical manifestations, the past history, the influence of treatment, mercurial or arsenical, makes it possible to differentiate between the two affections.

Clark,<sup>25</sup> in 1914, reported a case of undoubted involvement of the thyroid in a congenital syphilitic. The patient was a woman, 24 years of age, who five years previously had begun to suffer from palpitation and tachycardia and violent attacks of nervousness. At this time a swelling in the neck was also observed, although there was very little protrusion of the eyes. About one year later when the patient was first seen by Clark the clinical symptoms had become decisive and grew steadily worse until she fell into a drowsy, almost comatose condition with pulse over 200, paralyzed sphincters and continuous vomiting lasting a fortnight. Owing to the "Olympic forehead," the *crane natiforme*, and the history of epileptiform fits at 12 years of age, a Wassermann test was made. This was strongly positive as was one on the patient's mother.

Mercurial inunctions and epinephrin (1:1,000 solution, 20 drops three times a day) were prescribed, which resulted in a rapid cessation of the vomiting and in two days the patient had recovered consciousness.

In eight days the pulse was only 150, the thyroid smaller and the protrusion of the eyes better. After thirty inunctions, both the hyperthyroidic symptoms and the general health were much better. During the next month two injections of salvarsan (0.3 and 0.6 gm.) were administered and in three months the patient had quite recovered. She then returned to her home and the specific therapy

was discontinued. Twelve months later the symptoms reappeared and were again cured by similar treatment.

From the positive Wassermann in the mother, the virginity of the patient, the absence of clinical signs of infection, the presence of skeletal stigmata, and the history of epileptiform fits, Clark concluded this was a case of congenital syphilis.

#### PRESENT CASE

The following case came under my care during the past summer:

W. H. M., male, aged 72, widower, veteran of the Civil War and retired business man.

*Family History.*—A half sister died of cancer. The patient has four healthy children and there is no history of abortions or miscarriages of his wife who died about one year ago of pneumonia.

*Past History.*—Whooping cough as a boy and typhoid fever in 1865. Otherwise he has always been a healthy vigorous man. He absolutely denies all venereal infection, although he admits numerous opportunities for acquiring such infection before marriage.

*Present History.*—About four years ago the patient noticed a swelling of the neck, had palpitation and tachycardia, began to lose weight and felt weak. At this time he was examined by his family physician, a urinalysis being made, and was told that he had albumin in his urine.

He was given various kinds of medicine but steadily lost weight until he had fallen from 178 pounds four years ago to 127 at the present time.

*Present Complaint.*—Palpitation, indigestion and constipation.

*Present Examination.*—*Genitals* well formed. No scars on penis. Prostate only slightly enlarged. *Glands.*—No lymphatic glands are palpable. A tumor 10 cm. long x 4 cm. wide and apparently about 3 cm. thick is felt in the right side of the neck in the region of the right lobe of the thyroid. It is somewhat movable, is painless and is not tender. It causes the patient no discomfort, except that it compels him to wear a 17 inch collar instead of a 16. *Skin.*—The skin is somewhat wrinkled and several small pigmented moles are on the back. No scars present.

*Mouth.*—The right tonsil is somewhat enlarged and ulcerated. The teeth are all gone and replaced by false ones.

*Heart.*—The heart is very irregular and rapid (pulse 140) but no murmurs are audible.

*Arteries.*—The superficial arteries are palpable and hard.

*Blood Pressure.*—Systolic, 220. Diastolic, 120. Pulse pressure, 100.

*Lungs.*—Normal.

*Abdomen.*—Normal.

*Eyes.*—There is slight protrusion of the eyes. Vision is somewhat impaired. Eye-grounds, normal. Pupillary reactions, normal.

*Ears.*—Hearing somewhat impaired.

*Neurology.*—Negative.

*Urinalysis.*—Pale, clear, sp. gr. 1015, acid. Sugar, negative. Indican, negative. Albumin, 1.5 per cent. Many hyaline casts.

*Wassermann* strongly positive. (Even after being confronted with the positive Wassermann, which was repeated both in my own and in another laboratory, the patient denied any knowledge of venereal infection.)

Owing to the albumin and casts in the urine it was deemed advisable to administer specific therapy with great caution. He was therefore given daily intravenous injections of 0.005 gm. of mercury benzoate and potassium iodide by mouth, 10 drops in a half glass of milk t.i.d. one half hour after meals. This was increased 5 drops daily. The ulcerated tonsil was touched with 10 per cent silver nitrate solution daily. The Hot Springs baths were also prescribed, the patient remaining in the tub at 100° F. for 10 minutes and in the pack for 15 minutes. This induced full diaphoresis.

The urine was watched daily and in one week there was but a trace of albumin and only a few hyaline casts were found. There was also a perceptible diminution in the size of the tumor, while the pulse had fallen to 120 and the blood pressure to 200.

At this time the patient was given a small dose of salvarsan (0.2 gm.) intravenously. This caused an increase in the albumin and casts, so was not repeated.

The mercury injections and potassium iodide were continued for six weeks. When the dose of the latter reached 100 drops t.i.d. symptoms of iodism appeared. It was then discontinued for three days and begun again at 30 drops t.i.d.

At this time the patient was forced to return to his home. The tumor of the neck had decreased markedly in size until it was barely

palpable. The pulse had dropped to 85, and the blood pressure to 155. The urine still showed a trace of albumin and a few hyaline casts while the Wassermann was still strongly positive.

The patient was given a prescription for "mixed treatment" and advised to return in six months or to go to a well known syphilologist who lives near his home.

A letter received from him one month after his departure from Hot Springs stated that he had gained fifteen pounds in weight and felt better than he had for years.

#### CONCLUSIONS

1. Syphilis of the thyroid is a rare condition, but would probably be more often recognized if looked for more frequently.

2. It occurs both as an early and as a late manifestation.

3. It is apparently more frequent in women than in men and may occur at any age. It is a manifestation of congenital syphilis as well as of acquired syphilis.

4. The histological picture of the early involvement of the thyroid has not been described while that of the later involvement markedly resembles tuberculosis of this gland. There is an infiltration of round and epithelioid cells, the formation of fibrous tissue, giant cell formation, with proliferation and thickening of the vessel walls, even with obliteration. *Treponemata* have not been demonstrated.

5. The clinical picture may present nothing but tumefaction or there may be marked symptoms of goiter, exophthalmos, tachycardia, etc., or finally there may be so much pressure on the trachea and pharynx as to cause great dyspnea and hoarseness. Pain usually is absent.

6. The diagnosis must rest upon the history, the laboratory findings (Wassermann, luetin), and the improvement under specific medication, rather than upon the histological picture, unless the *Treponema pallidum* is demonstrated.

7. The prognosis will depend upon the date of the diagnosis. If recognized before marked symptoms occur, the prognosis should be good.

8. The treatment consists of antiluetic therapy, mercury, the iodides and salvarsan, or one of its substitutes, as well as symptomatic treatment.

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## THE PRACTICAL APPLICATION OF THE WASSERMANN TEST IN THE DIAGNOSIS AND CONTROL OF TREAT- MENT OF SYPHILIS\*

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SINCE 1909, the Wassermann test has been used in the army as a routine procedure in all cases suspected of syphilis and also very largely as a guide to the efficiency of the methods of treatment employed. More recently it has been added to the regular examination of recruits, which has resulted in our securing a fairly accurate idea of the prevalence of syphilis in various localities and among various classes of people. In this way a great mass of data has been accumulated regarding the value of this test, both in the diagnosis and as a control of the treatment of syphilis, and it is my purpose in this contribution to briefly discuss some of the more important practical points that have come under my observation during almost seven years experience with this diagnostic measure. It may be stated that the figures given and the conclusions arrived at are based upon the results of nearly 35,000 Wassermann tests personally performed and that the same technic has been employed in making all of these tests with the exception that, during the past two years, cholesterinized antigens have been used as well as antigens prepared from syphilitic fetal livers. A very careful comparison of the antigens has shown but very little difference in results, in my experience, and it is but rarely that I have observed a negative with one antigen and a positive with another. However, it is best to use both types of antigen with each test, if possible.

The technic employed, which is now generally adopted in the laboratories of the Army Medical Department, I have minutely described in a previous communication<sup>1</sup> and it will not be discussed here. It is essentially that recommended by Wassermann with the

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exception that a human hemolytic system is used instead of the sheep system.

In the army laboratories we use four designations for the result of the test. These are: Double-plus ( $++$ ), meaning a positive reaction, there being complete inhibition of hemolysis; Plus ( $+$ ), and Plus-minus, ( $+—$ ) doubtful reactions, there being a greater or lesser amount of hemolysis; and Minus ( $—$ ), or negative, there being complete hemolysis. A plus reaction is one in which there is at least fifty per cent of inhibition of hemolysis and corresponds to the three and two plus reactions of some writers.

It is now almost ten years since Wassermann, Neisser, and Bruck<sup>2</sup> published their description of what is now known as the Wassermann test and during this time it may be truthfully stated that no diagnostic test ever devised has received a more thorough trial or been subjected to a more searching analysis. It may also be said, with truth, that no test has ever suffered more in reputation from the use of it by the inexperienced and unscrupulous, for in some laboratories the test has been placed in the hands of poorly trained assistants or so-called serologists, who have neglected even the most essential precautions in performing what must be regarded as one of the most delicately quantitative tests used commonly in medicine.

However, at the present time, the general concensus of opinion is that, all in all, the Wassermann test is the most valuable aid that we possess in the diagnosis of syphilis, and although many unfortunate mistakes have occurred in the interpretation of the results of the reaction, and differences in results are noted in reports from different laboratories, due almost entirely to carelessness or inexperience in making the test, the fact remains that in this reaction we have what is probably the most valuable and generally useful diagnostic measure in the domain of medicine. The fact that, even in inexperienced hands, the test has often given correct results, proves its worth, and as Vedder<sup>3</sup> has well said: "One is impressed by the fact that the Wassermann reaction must be a test of most surprising merit to have survived all the clumsy technique that has been perpetrated in its name."

The exact nature of the reaction is still a mystery despite the immense amount of work that has been done in trying to solve this problem. We know, that as generally performed, it is not a true antigen-antibody reaction but a reaction between lipoids in the antigen and lipotropic bodies in the blood serum of syphilitics, but, on

the other hand, it has been demonstrated that a true antigen-antibody reaction may be obtained with the blood serum of certain syphilitics, because specific antigens, prepared from pure cultures of *Spirocheta pallida* give complement fixation when used with the blood serum of these individuals. That this latter reaction is in the nature of a group reaction was first shown by Nichols and myself,<sup>4</sup> for we found that alcoholic extracts of pure cultures of *Spirocheta pertenuis*, *Spirocheta microdentium*, and *Spirocheta refringens* gave complement fixation with syphilitic serum, while antigens made from *Bacillus typhosus* and *Spirillum cholerae* gave negative results. These observations have since been confirmed by Kolmer, Williams, and Laubaugh,<sup>5</sup> but the reaction with the specific antigen is most unreliable, as comparatively few cases of syphilis give a positive reaction and the trouble that might arise from its being a group reaction obviates its general use as a diagnostic measure in syphilis.

However, the fact that a specific complement fixation does occur in syphilis makes it probable that an antigen prepared from a fetal liver, rich in spirochetes, might give positive reactions in cases where the non-specific antigen is negative, and, for this reason, I am of the opinion that the Wassermann reaction, when an extract of fetal syphilitic liver is used as antigen is of a dual character, the reaction consisting in some instances, of a true antigen-antibody reaction and a non-specific reaction between the lipoids in the antigen and lipotropic substances in the patient's serum. When a non-specific antigen is used alone, the possible reaction between the true antibodies in the patient's serum and the antigen is lost, and thus the reaction may be negative when otherwise it might have been positive or suspicious. Accordingly I believe that both types of antigen should be used, if possible, but the antigens prepared from pure cultures of *Spirocheta pallida* have not been found reliable.

There are certain factors influencing the results of the Wassermann test which should be understood by physicians using this valuable diagnostic measure and these will be briefly discussed. Among the most important are the influence of alcohol and of the growth of certain bacteria in the blood serum to be tested, as well as the natural variation in the amount of inhibiting substances in the patient's serum.

*The Influence of the Ingestion of Alcohol.*—In 1911, Major Nichols and I<sup>6</sup> published observations regarding the effect of the ingestion

of considerable amounts of alcohol upon the result of the Wassermann test, and these observations have since been amply confirmed. In brief, we found that the ingestion of alcohol in the form of beer or whiskey, as well as alone, and in amounts varying from 180 to 240 c.c. of whiskey and 700 c.c. of beer, often converted a positive Wassermann reaction into a negative, and that the blood might remain negative for as long as three days, although generally it became positive again within twenty-four hours. In three of the original nine cases experimented with, the blood remained negative for twenty-four hours. Smaller amounts of alcoholic liquors will also render strong plus reactions negative and thus give a wrong impression regarding the efficiency of any treatment being pursued.

In all of the cases tested, the Wassermann reaction was double plus before the administration of alcohol, that is, there was absolute inhibition of hemolysis, while a few hours after the administration of the drug the reaction became negative. That this change in the reaction is not due to the actual amount of alcohol in the peripheral circulation is proved by the fact that a much larger amount of alcohol is necessary to produce hemolysis of the amount of blood corpuscles present in the suspension used than could possibly be present in the blood serum of the patients tested, for our experiments showed that if the blood serum of the patient had been absolute alcohol, the amount used would have been insufficient to have produced hemolysis. It thus appears that alcohol may render inert the substance or substances in the blood serum of syphilitics that give rise to the reaction, a point of great practical importance, as we have repeatedly found in the military service.

No specimen of blood for the Wassermann test should be collected without careful inquiry being made regarding the ingestion of alcohol within the last twenty-four hours before collection and if alcohol in any amount has been ingested the collection of the blood should be postponed. Even small amounts of alcoholic liquors may render a plus reaction negative and thus, where the test is being used as a control of treatment, obscure the real condition of the patient as regards his serological status.

*The Growth of Various Bacteria in the Blood Serum.*—I have shown that certain bacteria growing in specimens of blood serum may produce a false positive reaction with the Wassermann test. These observations were published in 1911<sup>7</sup> and proved that such

common organisms as streptococci and staphylococci, when developing in blood serum, may elaborate substances which will give rise to a positive Wassermann reaction. These substances require a temperature of about  $37^{\circ}$  C. for their development but this temperature may sometimes be reached in specimens of blood serum in the summer, even in temperate regions, and often in tropical localities. It was found that *Staphylococcus albus* and *Staphylococcus aureus* when growing at this temperature in blood serum sometimes produced a positive reaction and the same was true of a short chain streptococcus isolated from a blood serum. That every strain of a certain bacterial species will not produce this result was shown by the fact that while a double-plus reaction occurred in a serum infected with a stock staphylococcus and with an *S. aureus* isolated from a serum, a negative result was obtained with another *S. aureus* isolated from an infected serum which gave a negative reaction.

The fact that under certain conditions such common bacteria as those mentioned may give rise to false positive reactions when growing in blood serum might lead on to conclude that only fresh sera should be used in making the Wassermann test; but if proper precautions are taken during the collection of the blood there is no danger of contamination, and our experiments have shown that sera which are uncontaminated may be kept at room temperature for as long as a month without danger of a negative serum becoming positive, although often in sera kept for so long a time inhibitory substances develop which inhibit hemolysis in both the antigen and control tubes. Infected sera may be easily detected by their cloudy appearance and disagreeable odor and such sera should always be discarded.

The observations noted show that whenever the blood serum is to be kept for over 24 hours before the test is made, great care should be taken that the blood is collected aseptically. The needle or lancet used for puncture and the tube or other container in which the blood is collected should be sterilized, and the skin over the site of puncture thoroughly washed with alcohol or tincture of iodine applied.

*Variations in Amount of Complement Inhibiting Substance.*—Recent observations have shown that marked variations occur in the amount of the substance or substances in syphilitic blood serum which give rise to a positive Wassermann reaction. In 1914, I published<sup>4</sup> certain observations showing that in every stage of

syphilis variations occur in the blood serum from day to day sufficient to cause a double-plus, or positive, reaction to appear and disappear within so short a period of time as one week. The experiments proving this important fact were made upon prisoners at the U. S. Military Prison, at Fort Leavenworth, who were under most strict discipline and upon a routine diet, so that the question of the influence of alcohol upon the test could be absolutely excluded. Tests were made every day for a week in each case upon samples of blood collected on that day, and it was determined that titrations of these samples resulted in showing that great variations occurred in the strength of the Wassermann reaction, and that these variations must be taken into account in using the test in the diagnosis or as a control of the treatment of syphilis. The following tables illustrate the variations observed in the primary, secondary, and latent stages of the disease. The objections made by some writers that the variations observed were probably due to variation in the hemolytic system used are disproven by the fact that before each series of tests titrations were made of the reagents used, so that such variations were impossible.

TABLE I.

RESULT OF TITRATION OF BLOOD SERUM IN CASE OF PRIMARY SYPHILIS						
	Amount of Blood Serum c.c.					Control
Date of Test	0.02	0.04	0.06	0.08	0.1	0.1 c.c.
Nov. 19	+ -	+	+	+	+	-
Nov. 20	+ -	+ -	+	++	++	-
Nov. 21	+ -	+	++	++	++	-
Nov. 22	+ -	+ -	+	+	+	-
Nov. 23	+	++	++	++	++	-
Nov. 24	+ -	+	+	+	+	-
Nov. 25	++	++	++	++	++	-

N. B.—In these tables the sign ++ indicates a positive reaction, the sign + and + - doubtful reactions, and the sign - a negative reaction.

TABLE II.

RESULT OF TITRATION OF BLOOD SERUM IN CASE OF SECONDARY SYPHILIS						
	Amount of Blood Serum c.c.					Control
Date of Test	0.02	0.04	0.06	0.08	0.1	0.1 c.c.
Dec. 24	+ -	+ -	+	++	++	-
Dec. 25	-	-	-	-	+ -	-
Dec. 26	-	+ -	+ -	+	+	-
Dec. 27	-	-	+ -	+ -	+	-
Dec. 28	+ -	+	+	++	++	-
Dec. 29	-	+ -	+ -	+	++	-
Dec. 30	-	+ -	+	+	++	-

TABLE III.

RESULT OF TITRATION OF BLOOD SERUM IN CASE OF LATENT SYPHILIS						
Date of Test	Amount of Blood Serum c.c.					Control
	0.02	0.04	0.06	0.08	0.1	0.1 c.c.
Dec. 19	++	+	+	++	++	-
Dec. 20	-	-	+	+	+	-
Dec. 21	-	+	++	++	++	-
Dec. 22	-	+	+	+	+	-
Dec. 23	++	++	++	++	++	-
Dec. 24	++	+	++	++	++	-
Dec. 25	++	-	+	+	+	-

From a study of these tables it is evident that the strength of the Wassermann reaction varied widely in these cases from day to day. In the entire series of tests it was found that in one case of primary syphilis a plus or doubtful reaction was obtained on three of the seven days, the reaction on four days being double-plus or positive; in another case a plus or doubtful reaction was obtained on two of seven days. In one case of secondary syphilis a negative reaction was obtained on one day, a plus-minus on one day, a plus on three days, and a double-plus or positive reaction on two days; in another secondary case a plus or doubtful reaction was obtained on two of seven days. The other two secondary cases tested gave a double-plus or positive reaction on each of the seven days.

Of the latent cases tested, one gave a plus-minus reaction on two days and a plus or doubtful reaction on four days of the week, a positive reaction being obtained on only one day; another gave a negative reaction on one day, a plus-minus on another, and a plus reaction on three days, a positive reaction being obtained on only two of the seven days; while the fourth case gave a double-plus or positive reaction on all but one day of the seven.

These observations indicate that, whatever are the substances producing complement fixation in syphilis when a non-specific antigen is used, they must be present in a certain amount before a positive Wassermann reaction is possible, and that this amount varies considerably from day to day. The important point, from a practical stand-point, is that untreated cases of syphilis may give a positive reaction on one day and a negative upon the next because of this variation in complement binding substances in the blood serum. The results also show how valueless a single negative Wassermann reaction is in eliminating syphilis in a suspected individual.

It is but just to call attention to the importance of these results in explaining, possibly, the discrepancies between Wassermann reports from different laboratories where specimens of blood from the same case are examined at different times, and where a positive result is reported from one laboratory and a negative from another. Unless the same specimen of blood be examined no reliable conclusions can be drawn regarding the reports of different laboratories, a fact that should be borne in mind when it is desired to obtain the report of more than one laboratory upon a suspected individual.

Besides the factors which have been mentioned there are certain features connected with the technic of the test that are of immense importance. Thus the quantity of blood serum tested with the particular method employed must be strictly adhered to, for normal blood serum will give a positive reaction if too much be used and positive sera may be negative if too little be used. The maximum dose of serum must be ascertained for each technical method and should never be exceeded and the use of an amount exceeding the maximum should not be considered as allowable even if certain normal sera may react negatively when this amount is used.

The titration of the guinea pig serum used as complement is of vital importance, and this should be done before each series of tests is made. Guinea pig serum varies very greatly in complementary power and anyone who undertakes to use the same amount of this serum for every series of tests will make grievous errors and many innocent individuals will be diagnosed as syphilitic. Although this is true, it is remarkable in how many laboratories this fundamental part of the technic is omitted. The Wassermann test is absolutely quantitative in nature and unless all of the reagents used in the technic are accurately titrated at frequent intervals, erroneous results are sure to occur. For this reason the physician should be acquainted with the factors influencing the reaction, and the importance of accuracy in the technic, in order to avoid sending his patients to laboratories where there is any doubt of the scientific training of those employed in making the Wassermann test.

Among the practical questions which the general practitioner often desires answered regarding the Wassermann reaction are whether or not it is specific; the percentage of positive results that may be expected with it in the various stages of syphilis; the date

of appearance of the reaction; and the interpretation that is to be placed upon the various degrees of the reaction as reported from the laboratory. These points will now be considered.

*The Specificity of the Wassermann Reaction.*—It must be confessed that the Wassermann reaction is not absolutely specific for syphilis, for positive results have sometimes been observed with other diseases. While this is true, the fact remains that a positive reaction indicates syphilis in so immense a proportion of individuals giving it that the practical value of the test is hardly at all decreased by the few instances in which such a result is obtained in other conditions. As our knowledge of the technic of the test and of the factors controlling its results, has increased, these non-specific reactions have become fewer and fewer and now we know that a positive reaction with the test occurs in but a very few conditions that are not syphilitic. Any serologist who reports a large number of positive reactions in conditions other than syphilitic proclaims that his Wassermann technic is poor, for, if perfectly performed, this test gives positive results in very few non-syphilitic conditions. Among these may be mentioned some malarial infections, during the febrile stage; yaws, a disease closely related to syphilis and caused by a spirochete; relapsing fever occasionally; some cases of leprosy; and diabetes in those cases in which acidosis is present. It has been reported as positive in numerous other conditions, as scarlet fever, pellagra, septic infections, etc., but recent researches have proved that most of these positive reactions were the result of imperfect technic and erroneous reading of the test.

In my own experience, I have obtained twelve positive reactions among 4,000 individuals suffering from diseases other than syphilis or 0.3 of 1 per cent. Of these patients five were suffering from tertiary malarial infection and gave a positive result during the febrile stage, which became negative when the temperature returned to normal; three were diagnosed as tuberculosis; three as pityriasis rosea; and in one the diagnosis was undetermined. In the pityriasis rosea cases the reactions were almost double-plus but would not have been returned as positive without a qualifying statement, while in two of the tuberculosis cases a history of syphilitic infection was afterward obtained. But, even admitting that all of these cases gave a false positive reaction, the real value of the test is little affected as a diagnostic measure. Vedder<sup>9</sup> has obtained similar results, ob-



taining four positive reactions among 1,049 individuals suffering from other diseases than syphilis, or 0.4 of 1 per cent. Thus, while it cannot be claimed that the Wassermann test is, when positive, absolutely specific of syphilis, from a practical standpoint it is doubtful if a more specific test is used in medicine, the margin of error appearing to be less than 0.5 of 1 per cent.

*The Percentage of Positive Results in the Various Stages of Syphilis.*—The practitioner, in submitting a specimen of blood to the serologist for this test naturally desires to know in how large a proportion of cases such as the specimen has been obtained from the Wassermann test is positive. A large amount of data has accumulated regarding the percentage of positive results obtained in the various stages of syphilis and there is a remarkable uniformity among serologists as to this question, thus proving the reliability of the test in many different hands. My own experience is practically that of all others who have handled the same or approximately the same number of cases and the results are given in the following table:

TABLE IV

THE RESULTS OF THE WASSERMANN TEST IN 5,600 CASES OF SYPHILIS					
Stage	Total Cases	Positive	Per cent	Negative	Per cent
Primary	1080	970	89.8	110	10.1
Secondary	2217	2132	96.1	85	4.9
Tertiary	728	633	87.4	95	13.5
Latent	1525	1039	68.1	486	31.8
Congenital	28	25	82.2	3	10.7
Parasyph	22	15	68.1	7	31.8
Totals	5600	4814	85.9	786	14

In considering this table it should be remembered that in at least 95 per cent of the above cases only one Wassermann test was made and had repeated tests been performed it is undoubtedly true that a higher percentage of positive results would have been obtained in all the stages of syphilis tested. However, for practical purposes it may be stated that we must expect about 10 per cent of negative results in the primary stage of the disease; about 5 per cent in the secondary stage; about 13 per cent in the tertiary stage; and about 30 per cent in the latent cases. The figures given regarding congenital and parasyphilite cases are not reliable as the cases are too few in number, but the researches of numerous in-

investigators show that we may expect about 95 per cent of positive reactions in the blood of congenital syphilitics; about 98 per cent of positives in paresis; 70 per cent in tabes; and 50 per cent in cerebrospinal syphilis.

*The Date of Appearance of the Reaction in Syphilis.*—The date after infection when we may expect the Wassermann reaction to be positive is a point of great practical interest, for we know that the earlier treatment is commenced in syphilis the better are the results, and unless the Wassermann test can assist us in making a diagnosis early in the disease, it loses much of its value as a diagnostic measure. While the ideal method of diagnosing syphilis in the primary stage is by the finding of the spirochetes with the dark field apparatus, this measure is sometimes unsuccessful, especially if local treatment has been given the initial lesion, and comparatively few practitioners possess the apparatus. From my personal experience I believe that the Wassermann reaction is a most valuable aid in diagnosis even thus early in the disease and I cannot agree with those writers who claim that in the primary stage of syphilis the Wassermann test is of little value. In my own experience, nearly 90 per cent of primary cases have shown a positive reaction, if repeatedly tested, before the appearance of secondary symptoms, and while a single test, performed at a very early date after the appearance of the chancre will be negative in a large number of cases, repeated tests will prove that the reaction becomes positive before the appearance of secondaries in the vast majority of cases.

The following table, compiled from personal observation, gives the date of appearance of the positive reaction in periods of weeks after the appearance of the initial lesion, based upon 600 cases of primary syphilis in which the data could be accurately ascertained.

TABLE V

DATE OF APPEARANCE OF WASSERMANN REACTION IN WEEKS IN 600 CASES OF PRIMARY SYPHILIS					
Week after Appearance of Chancre	Total Cases	Positive	Percent	Negative	Percent
First week	77	27	36.3	50	64.9
Second week	155	92	59.3	63	40.3
Third week	158	109	68.9	49	31.
Fourth week	167	129	77.2	38	22.7
Fifth week	43	35	81.3	8	18.6

From this table it will be seen, that in my experience, 36 per cent of primary cases of syphilis have given a positive Wassermann reaction within the first week after the appearance of the chancre; almost 60 per cent during the second week; almost 70 per cent during the third week; over 77 per cent during the fourth week; and over 80 per cent during the fifth week after the chancre appeared. It is evident, therefore, that the Wassermann test is of very distinct value in the diagnosis of syphilis during the primary stage and should be employed whenever the spirochetes cannot be demonstrated. In the army, because of the availability of the test, owing to the situation of the Department Laboratories of the Medical Department, every suspected case can be examined at weekly intervals, if necessary, and thus the diagnosis is generally established early in the disease. This cannot be done generally in private practice owing to the cost of the test; but in cities where the city laboratory is prepared to do Wassermann work every patient having a sore upon the penis should be repeatedly tested, provided, of course, the dark field apparatus is not available, or examinations with its aid are negative.

Modern research upon syphilis has proved that the morphology of a sore upon the penis is of little value in diagnosis, as the typical Hunterian chancre is almost as much the exception as the rule, and mixed infection with chancreoid sores are so common. The best authorities upon the disease admit that it is impossible, in many instances, to differentiate the primary syphilitic lesion from other sores by its clinical characteristics, and, for this reason, every suspicious case should be subjected to the Wassermann test, and, if possible, a dark field examination repeatedly made. The old idea that it is best to let the case go undiagnosed until the appearance of secondary lesions is no longer countenanced and the physician who pursues this course is criminally negligent, for with the Wassermann reaction and the dark field apparatus practically every case of primary syphilis may be diagnosed before it is time for the secondary lesions to appear.

*The Interpretation of the Wassermann Reaction.*—In a previous communication I have considered in detail the interpretation of the results of the Wassermann test and here will only touch upon the most important facts concerning the subject. There are many misconceptions prevalent in the profession regarding the exact value

to be placed upon the various types of reaction reported by various laboratories, and the value of a negative reaction in excluding syphilis, with the result that a single negative reaction has often been, and is, considered as definitely excluding syphilis, while a positive diagnosis of the disease has been based upon a plus or plus-minus reaction, even where symptoms were absent and the history was negative. Such interpretation of the results of the Wassermann test are absolutely unwarranted and for this reason it is most important that the physician have a clear conception of the meaning of the terms employed by laboratories in reporting upon the test. It is unfortunate that different laboratories employ different terms, as this causes confusion in many instances, but if the terms employed by the laboratory to which the physician sends his tests are understood little harm is done. In the army, as I have stated, we employ four designations in reporting the test, double-plus ( $++$ ) indicating complete inhibition of hemolysis, and therefore, a positive reaction; plus ( $+$ ), indicating anything between complete inhibition and 50 per cent of inhibition of hemolysis; plus-minus ( $+ -$ ), indicating anything between 50 per cent of hemolysis and complete hemolysis; and minus ( $-$ ), indicating complete hemolysis, and therefore, a negative reaction. Plus and plus-minus reactions are always considered as doubtful reactions in the absence of a clear history of infection or of definite symptoms of the disease.

In many laboratories the results of the test are recorded as four-plus ( $++++$ ) indicating complete inhibition of hemolysis, and three-plus ( $+++$ ), two-plus ( $++$ ), and plus ( $+$ ) indicating lesser degrees of inhibition. Comparing these designations with the ones employed in this laboratory, the three plus and two plus would correspond to our plus, while the plus would correspond to our plus-minus.

As a result of our studies of syphilis in the army the following conclusions appear to be valid regarding the interpretation of the results of the Wassermann test:

1. If the diseases, other than syphilis, that sometimes have given a positive result with the Wassermann test, can be excluded, a double-plus (four-plus of some writers) reaction is diagnostic of syphilis. Under such conditions I consider this type of reaction as absolutely specific, whether symptoms are present or not, or whether there is or is not a history of infection.

2. Under the same conditions, a plus reaction (three-plus or two-plus of some writers) may, in primary, tertiary, and latent infections be regarded as diagnostic, provided there is a clear history of infection, or suspicious clinical symptoms are present. In the absence of either history or clinical symptoms a plus reaction should not be regarded as diagnostic of the disease.

3. A diagnosis of syphilis should never be made upon a plus-minus reaction. Many perfectly normal individuals give this type of reaction and it is of no value in the diagnosis of the disease except that it should be considered as negative.

4. A single negative reaction, where there is no history of infection and where symptoms are not present, is of considerable value as a corroborative sign of the absence of syphilis, but where there is any suspicion that the disease may be present it has very little value in excluding syphilis. The experiments already mentioned upon the variation in the complement binding power of the serum of known syphilitics illustrates the truth of this statement and it is only when a negative reaction is repeatedly obtained over a long period of time that it can be considered as good evidence of the absence of the disease, and even then the spinal fluid should be tested and a provocative Wassermann test made upon the blood, if possible. The same remarks are true of treated cases, a single negative reaction being of no value as indicating cure. A provocative Wassermann test should be made after the reaction has remained negative for at least a year without treatment, and if this is negative, the spinal fluid should be tested. In certain cases a luetin test also should be made before the patient is considered as cured.

The interpretation of the results of the Wassermann test must rest very largely with the clinical picture present and it is the clinician's place to reconcile the result of the test with the clinical picture rather than the serologist's. The latter simply reports what actually occurs when the patient's blood serum is tested, and it remains with the clinician to interpret the report in the light of his patient's history and symptoms.

*The Provocative Wassermann Reaction.*—The provocative Wassermann reaction has been mentioned as a test for the cure of syphilitic infection and a few words regarding its use may be of interest from the practical view-point of the application of this test.

Gennerich<sup>11</sup> was the first to call attention to the fact that patients

previously treated with salvarsan and giving a weak or negative Wassermann reaction often became strongly positive after a small dose of the drug, the blood being tested daily for a week after its administration. The positive reaction generally occurred within 48 hours but sometimes it was delayed for as long as 7 days. His observations were soon confirmed by numerous authorities and the provocative Wassermann test has been used quite extensively as a test of whether or not a patient is cured of syphilis.

In my own experience this test has repeatedly proved positive in cases that had given a negative reaction in the blood for long periods of time and I regard it as a valuable method of determining whether a negative reaction present with the ordinary Wassermann is an index of the absence of the spirochetes. The following table illustrates the results obtained by this test in cases that have presented a negative Wassermann reaction for many months:

TABLE VI

RESULTS OF THE PROVOCATIVE WASSERMANN TEST IN SYPHILIS			
Case No.	Time Since Treatment	Result of Wassermann Test	Result of Provocative Test
1	Months—15	—	++
2	Months—16	—	—
3	Months—17	—	++
4	Months—18	—	++
5	Months—19	—	++
6	Months—21	—	—
7	Months—24	—	—
8	Months—24	—	—

From this table it is evident that cases of syphilis that had given a negative ordinary Wassermann test for as long as 17, 18, and 19 months reacted positively after the administration of salvarsan, thus proving that the infection was not cured. In the army the provocative test has been used quite extensively as a control of cure and the results have been very satisfactory, but the test is also very valuable in the diagnosis of syphilis, in those cases that are suspicious and yet give a negative ordinary Wassermann reaction. In my own experience I have observed several early primary cases, in which the Wassermann was negative, and which reacted positively after a dose of 0.3 to 0.4 gm. of salvarsan intravenously. It is my belief that we have not availed ourselves of this method of diagnosing syphilis to the extent that we should have done and that its use in primary

infections, during the first week or two after the appearance of the chancre, would result in a great increase in the number of positive reactions at this stage of the disease and consequently in better therapeutic results because of earlier diagnosis. Also in other stages of syphilitic infection in which the ordinary Wassermann test is negative, the provocative reaction will often be found of the greatest value in diagnosis.

It is not necessary to give a full dose of salvarsan for this purpose, as doses of 0.3 to 0.4 gm. are sufficient and a great advantage of this method is that, if the disease is syphilitic in nature, we are applying a most valuable therapeutic as well as diagnostic measure. It is a method of diagnosis that should be used whenever practicable, especially in early primary infections.

*The Wassermann Test as a Control of Treatment.*—In the army the Wassermann reaction has been of the greatest value in testing the efficiency of various methods of treating syphilis and has been very largely used for this purpose. As an illustration of this it may be stated that, in my own experience, I have made almost twenty thousand Wassermann tests upon treated patients, all of these tests for the purpose of controlling the treatment, and my experience has been that of all other medical officers who have had charge of the army laboratories where the Wassermann test is made.

Aside from its value as a diagnostic agent, the greatest value of the complement fixation test for syphilis is found in its use as a control of treatment. By means of this test, repeated at frequent intervals, one is able to diagnose relapses of the infection long before the appearance of clinical symptoms in the vast majority of cases. In this way we are able to treat the infection before it has produced the symptoms of relapse and obviously at a stage when it is more amenable to treatment than after gross clinical symptoms have appeared. I believe that it may be stated with truth, that, in the vast majority of cases, the first symptom of relapse is the recurrence of a positive Wassermann reaction, and that this recurrence may be present weeks or even months before marked clinical symptoms are noticed. For this reason all cases of syphilis that have been treated should be tested at frequent intervals in order to ascertain the effect of the treatment upon the reaction, and after a negative reaction is obtained, a test should be made at least every three months, for a period of a year, when, if the test is still negative,

a provocative Wassermann test, a Wassermann upon the spinal fluid, and a luetin test should be made, before any patient is pronounced cured.

The data derived from the use of this test in the control of the treatment of syphilis has enabled us to use both mercury and salvarsan intelligently and has added much to our knowledge of the action of other drugs that have been advocated from time to time in the treatment of the disease. It has shown that the absence of symptoms is no criterion of cure in this disease, even though they may be absent for months or years, and that the physician who bases his prognosis upon clinical evidence in syphilis will often be greatly disappointed.

*The Wassermann Test upon the Cerebrospinal Fluid.*—It is now a well known fact that while the Wassermann test may be negative in the blood, it may be positive in the cerebrospinal fluid. It was formerly believed that if the reaction was negative in the spinal fluid and positive in the blood, it indicated the presence of cerebrospinal syphilis, where nervous symptoms were present, but it is now known that if enough of the cerebrospinal fluid is tested, the reaction will be found positive in practically all cases of cerebrospinal syphilis as well as paresis. In cerebrospinal syphilis the Wassermann reaction in the blood is often negative, while in paresis, the reaction in this fluid is almost always positive. These facts should be borne in mind in differentiating between the two conditions with the Wassermann test.

The fact that many instances have been observed where the Wassermann test is negative in the blood and positive in the cerebrospinal fluid, even when no symptoms of involvement of the central nervous system are present, renders this test of immense importance in the examination of the spinal fluid, aside from its value in detecting the nature of the nervous involvement. No patient can be truthfully stated to be free from syphilitic infection unless both the blood and cerebrospinal fluid give a negative Wassermann reaction and this procedure should never be omitted when the question of the cure of the disease is to be decided.

In paresis the test is positive in the blood and cerebrospinal fluid in practically 100 per cent of cases if 1 c.c. of the fluid be used in the test, while if smaller quantities are used, the percentage decreases, until, when but 0.2 c.c. is used, only about 75 per cent of paretis will show a positive spinal fluid. The same statement holds good with



patients suffering from cerebrospinal syphilis, nearly 100 per cent giving a positive reaction with 1 c.c. of the spinal fluid but only about 10 per cent if 0.2 c.c. is used. It will thus be seen that in order to use the test in differentiating cerebrospinal syphilis and paresis it is necessary to titrate the spinal fluid, and that, in most instances, a positive result with but 0.2 c.c. of the fluid is diagnostic of paresis.

In tabes the spinal fluid is positive in only from 5 to 10 per cent of the cases if 0.2 c.c. be tested but if 1 c.c. be used it is positive in at least 95 per cent of the cases. In this disease the Wassermann reaction in the blood is positive in about 70 per cent of the cases. The results of the Wassermann test in the cerebrospinal fluid rest wholly upon the amount of the fluid tested and it is necessary to use 1 c.c. if accurate results are obtained. However, in differentiating between tabes, cerebrospinal syphilis, and paresis, smaller amounts should be used and an accurate titration of the fluid made, as only in this way can the test be of value in differential diagnosis. In addition the cell count and the amount of globulin should be ascertained, but the lack of space forbids the discussion of these very valuable aids in the diagnosis of syphilis of the nervous system.

*Conclusion.*—There are other factors entering into the practical application of the Wassermann test to the diagnosis and treatment of syphilis that might be discussed with profit but it is hoped that those considered in this paper will prove of service to the practicing physician and render more clear the value and the limitations of this test. At the present time it may be stated that the diagnosis of syphilitic infections and the proper control of their treatment is based upon the results of serological examinations, to a very great extent, and that the physician who neglects the use of these methods is doing a great injustice to his patients. The Wassermann test has made possible the diagnosis of syphilis in individuals in whom no visible signs of the disease have been present for many years, and has rendered the differentiation of syphilis from other diseases of the central nervous system certain and practical. In addition it has proved that many of our clinical conceptions of the disease were erroneous and that the ease with which it was supposed to be cured by mercury and other drugs, including salvarsan, is a dangerous fallacy. The test has been most thoroughly investigated and despite the fact that it has been greatly injured in reputation by careless technique in the hands of inexperienced laboratory assistants, it stands to-

day as the one most generally useful method that we possess in the diagnosis of syphilis and as a control of the treatment of the disease. If some method of standardization of the test could be adopted by all serologists it would render it even more valuable, but the technical difficulties in the way of such a standard are very great and it is doubtful if all serologists would agree to any one technic for the test.

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## A PLEA FOR ROUTINE WASSERMANN EXAMINATIONS FOR OBSTETRIC AND GYNECOLOGIC PATIENTS IN HOSPITAL AND GENERAL PRACTICE

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THE diagnosis of syphilis in women is more difficult than in men so far as the recognition of the initial lesion of the disease is concerned. Even when the chancre is situated on the external female genitals it may escape notice or be judged insignificant by both patient and physician because in women the chancre is smaller and not as indurated as is the initial lesion in the male. Furthermore, the scar of the primary lesion in women is less marked and therefore, less recognizable than in men. Palmer from his examination of 600 syphilitic women, in the majority of whom the time of the primary infection was known, found that the scar of the primary lesion was recognizable on the skin of the external genitals for only about six months, while it had entirely disappeared by this time on the mucous membranes. In a considerable proportion of cases the initial lesions in women are about the cervix or upper vagina, where for obvious reasons they are not recognized or are confounded with other lesions.

As a consequence of the above, syphilitic infection in women is either overlooked or passed over lightly by the gynecologist or treated by the obstetrician in a haphazard manner, when the evidence of the disease is unmistakable in either mother or fetus. Our professional responsibilities today, however, regarding this most prevalent and serious disease are far different from what they were ten years ago before the discovery of the *spirocheta pallida*, the Wassermann reaction, and salvarsan. With diagnosis and treatment established on a scientific and, therefore, satisfactory basis, the specialist and practitioner are just as much, if not more, to blame for failure to detect syphilis in a given patient than they would be to overlook diabetes, tuberculosis, or cancer.

It is generally believed that syphilis is more common among men than among women. Pusey and Pollitzer, from the result of their observations, believe lues to be two or three times more common in men than in women. Hubert, on the other hand, from careful histories of possible luetic infection combined with routine Wassermann tests, found in between eight and nine thousand patients examined, that the proportion of syphilitics among the women was one-half per cent higher than among the male patients. It will require some years of careful statistical study of syphilis with modern diagnostic methods before we will be in a position to know definitely in which sex the disease is more prevalent. It may well be that many cases in women have been overlooked for reasons already mentioned and because women, far more than men, shrink from being examined for syphilis. Routine blood examinations where the patient remains in ignorance of the purpose of such examination may very well in the next few years change our opinions regarding the frequency with which the two sexes are affected. But after all, this question is for future investigation. If, as seems probable from conservative figures, there are between 3,000,000 and 4,000,000 syphilitics in the country at the present time, a far more important question for the practitioner to consider is who among his patients are afflicted with this most serious disease and how they are to be cured.

The more the Wasserman test has become perfected, the less liable to error, and the more valuable has it become. Buhman in an article read at the 1916 meeting of the American Gynecological Society from the result of his investigations at the St. Louis Barnard Free Skin and Cancer Hospital comes to the following conclusions: that, while theoretically the Wasserman reaction is not specific, practically it is highly specific; a strong positive reaction with proper controls and accurately titrated reagents is conclusive evidence of syphilis; the diagnosis of syphilis cannot be made upon a weakly positive reaction without some clinical evidence of the disease; a negative reaction does not exclude a syphilitic infection; malignant diseases do not give positive reactions.

As a clinician I am in hearty accord with these conclusions. No valuable laboratory test has ever been introduced that has not been attended by certain possible sources of error. After all, the value of any test is dependent upon the human element. Tests in certain laboratories are as reliable as any tests can be, but they are

never infallible. Hence, the necessity of supplementing, not only the Wassermann, but all laboratory tests with the most careful clinical observations. Especially true is this when the test is merely suggestive of a serious disease. I have always maintained that the clinician has the right to employ even radical treatment upon clinical evidence alone, even when unsupported by laboratory findings. On more than one occasion have I removed the uterus for clinical reasons when the microscopic examination of the curettings was negative for carcinoma. Subsequent examination of the removed uterus in most instances has shown by the presence of cancer the wisdom of the procedure.

Last May I presented before the American Gynecological Society some observations on the occurrence of syphilis in the University of Michigan Obstetric and Gynecologic Clinic and additional observations have been made for this paper. It is a hospital rule that every in-patient at the University Hospital should have a Wassermann made, although up to date it has been found impossible to comply strictly with this rule. However, enough of such examinations have been made to furnish some very interesting data regarding the prevalence of syphilis in a hospital population neither rich nor very poor and, consequently, resembling the patients in the average general practice. By an unwritten rule of the hospital all patients with syphilis or where such a diagnosis is suspected are referred for examination to the Department of Syphilology. The referred patients are most carefully examined by trained specialists in this department who pronounce the case luetic, non-syphilitic, or doubtful, in accordance with the physical findings plus the results of the Wassermann tests. It is apparent that figures based upon such examinations must be fairly accurate and of considerable value.

It was found that there were 18 undoubted cases of lues in 381 obstetric patients examined, or 4.7 per cent. It was stated at the time that subsequent reports might show a decidedly higher proportion of syphilitics in this clinic and that this is true is shown by the examination of 96 additional obstetric patients where there were 10 undoubted cases of syphilis or a percentage of 10.4 over twice as high a percentage as in the first series. However, percentages based upon such a small number of cases are relatively of very little value. A better idea of the prevalence of syphilis in obstetric patients of this kind may be obtained by adding the two together. Thus in 477 obstetric patients there were 28 undoubted cases of syphilis, or 5.8

per cent. While this probably is a higher percentage than will be found in the average private obstetric practice, the proportion would not probably be much higher if the same careful tests were made in an equal number of private patients; for the patients making up this clinic are not unduly exposed to syphilis since they are not prostitutes but country girls, waitresses, domestics, stenographers, etc.

While it is too much to hope for in the ordinary obstetric practice, it would be interesting to make Wassermann tests in an equal number of cases and study the results. Undoubtedly a surprising number of patients would give positive tests even when there was no history of lues. In the 28 syphilitics out of the 477 patients examined there were only 12 who gave positive histories of infection. Eight out of these twelve patients gave 4 plus Wassermans, one, a 2 plus while three were doubtful, or plus minus. Such findings show the necessity of not limiting the Wassermann examinations to the obstetric patients who give histories of syphilitic infection, but to look forward to the time when every pregnant woman will have her blood tested, just as today every careful practitioner insists upon frequent examinations of the urine. May the time be not far distant when routine blood tests may be made without wounding the sensibilities of the average patient. The word syphilis has been for so long a word to be whispered and has carried with it such reproach and shame, even when the patient be innocent of any breaking of the moral law, that it will be a long time before lues can be treated on the same basis as other diseases. Yet all recent experience goes to show that in the Wassermann test we have a valuable aid in diagnosing unsuspected lues and giving the mother and her unborn child the benefit of the proper treatment at the right time.

It must be borne in mind that the patients in this series were questioned as to the possibility of luetic infection by men trained in such work and for that reason the fact that 16 out of 28 syphilitics gave absolutely no history of infection counts for more than where the statistics are based upon the usual careless history taking, so common in private practice where the practitioner has little time for such work. In those cases where the histories were doubtful all gave 4 plus Wassermann tests. In those giving negative histories of luetic infection, eight gave 4 plus Wassermans, one 3 plus, two were 1 plus, while in two cases the evidence of maternal syphilis was obtained by physical examination of the mother and microscopic ex-

amination of the placenta and fetus. Again, it must not be lost sight of that a much larger percentage of patients in private practice would give negative histories of infection since they could not be questioned as closely as could the patients in the Maternity Service. This is another argument in favor of routine blood examinations in private practice, and not limiting such examinations to those giving histories of possible luetic infection. Unsuspected syphilis in the pregnant, as well as the nonpregnant woman, is a misfortune in that valuable time is lost for instituting treatment whereby both mother and child may be cured or at least benefited.

It has already been pointed out that careful physical examination of the woman with syphilis may reveal no signs of the disease. At least this is true of the ordinary examiner, while it is equally true that the syphilologist may find more evidence of the disease. However, since it is manifestly impossible to refer every pregnant patient to the specialist, the fact that the physical manifestations of the disease in question escape the attention of the practitioner is another argument in favor of routine Wassermanns in obstetric practice.

Only 11 of the 28 syphilitic patients, or less than half, showed evidence of the disease even after the most careful physical examination. Naturally these patients showed a large number of 4 plus Wassermanns, eight out of the eleven; while of the other three, one gave a 4 plus, two being plus minus or doubtful. However, the most interest centers on the 17 cases where no physical signs of syphilis were discovered. In four cases where the physical signs were doubtful, the Wassermann tests were 4 plus, while of the remaining 13 cases of syphilis, but without physical manifestations of the disease, 7 gave 4 plus Wassermanns, one a 3 plus, two a plus, while the Wassermann was negative in three, the diagnosis being made from other circumstances connected with the cases. It must not be forgotten that the physical examinations referred to above were made by members of the obstetric staff, not by the syphilologists. Naturally, the signs of the disease were more apparent to the specialist than to those working along another line. Still, for the general practitioner the report as given is of more value as showing the number of obstetric patients with syphilis who gave no physical signs of the disease.

Much interest centers about the treatment of the pregnant woman with syphilis. A review of the literature seems to show that the

treatment of the syphilitic pregnant woman with mercury or salvarsan or both is beneficial to the mother and fetus. However, it must not be overlooked that salvarsan is not a remedy which can be used without discrimination. The drug undoubtedly in some cases gives rise to albuminuria, rise in temperature, increase of blood pressure and signs of toxemia. In some instances undoubtedly, abortion is produced or hastened by the drug, although it is well not to be dogmatic in such statements since abortion is so frequent from the disease itself where no drugs have been administered. Potassium iodide in large doses is indicated for the late stages of syphilis in the pregnant as well as the nonpregnant woman. We must be careful to take into consideration the time of infection in judging of the effect of maternal antisyphilitic treatment upon the fetus. If the mother be infected early in pregnancy it is fair to assume that antisyphilitic treatment has been successful if she carries the child to full term and the living child shows no signs of the disease. On the other hand, it does not necessarily follow that the escape of the child where the mother has been infected late in her pregnancy, the eighth or ninth month, has been due to antisyphilitic treatment, since the child may not be infected by syphilis contracted at these late stages of pregnancy. But in the interest of the mother and because it is never absolutely certain how long it may take for the spirochetes to pass through the placenta, antisyphilitic treatment should be instituted at all periods of gestation.

Treatment of the patients in the maternity service who were suffering from syphilis compared with those not treated seemed to show that the greater proportion of those receiving treatment were delivered of living, full-term children. Here again, one must be careful in arriving at conclusions without taking into consideration all the facts. The same types of cases must be taken if results are to be compared. It is well known that women with long standing syphilis have a better chance to give birth to living children than do those where the infection is recent.

While at the present time, as has been stated, it is too much to expect that all pregnant women be given the Wassermann test, at least those who have had one or more miscarriages should be thus examined. To be sure, many miscarriages are due to other causes, but syphilis is such a common cause of the interruption of pregnancy that such a possibility should always be borne in mind. A



macerated fetus should be judged syphilitic until microscopic examination has failed to show signs of the disease, and the mother's Wassermanns have proved negative. Colles's law, that the healthy mothers of syphilitic children may nurse their children without contracting the disease, has been shown to be untrue in recent years. The mother does not acquire syphilis from her child because she already has syphilis as shown by many hundreds of serologic examinations. Under some circumstances a healthy child can be born of a syphilitic mother, but the mother of every syphilitic child also has the disease. Hence there is no excuse for the destruction of any still-born fetus. Such material should be examined by a competent pathologist for evidence of syphilitic disease, at the same time that the mother is subjected to a careful Wassermann test.

The results of the Wassermann examinations of newborn infants by collecting the blood from the placental end of the cord has not proved highly satisfactory, for only a very small proportion of children, undoubtedly syphilitic, give positive tests. This may have been due to the antisyphilitic treatment employed prior to the confinement for in three instances where such treatment was omitted the children's reactions were positive. The discussion of just why the test fails in newborn infants, undoubtedly syphilitic since they were the offspring of syphilitic parents, need not be gone into here. Although we are endeavoring to obtain the spirochetes from the umbilical cord immediately after the birth of the child, up to the present time we have not been very successful. Fortunately, positive tests are not absolutely essential in the case of the newborn infant, since we can reach certain conclusions regarding the condition of the child from the serologic examination of the mother. A child born of a syphilitic mother must always be judged syphilitic until repeated tests have failed to reveal any evidence of the disease. Not only do children of syphilitic mothers acquire the disease through the placental circulation, but in the cases of maternal infection late in pregnancy where probably the time, prior to the birth, is too short to allow the passage of the spirochetes from the mother to the child, the latter may acquire the disease during its passage through the birth canal. Under such circumstances Wassermann tests will be negative at birth but active syphilis will show itself later. These are exceptional cases, for fetal infection in the great majority of cases occurs through the placental circulation; hence it follows that

if the mother be syphilitic the chances of the fetus escaping infection are comparatively slight.

Hereditary syphilis may manifest itself at any time during life, although such manifestations are much more frequent during the early years of life. Given an infected mother, the practitioner's duty is clear. He should always be on the watch for the disease in the child, who should be subjected to frequent serologic tests. Upon the practitioner rests the responsibility of discovering the disease in the child early and seeing that the proper treatment be instituted. While this is not the time to discuss the question, it may be well in passing to state that it is the duty of the state to care for all dependent syphilitic children of no matter what age. The infants of syphilitic parentage cannot be placed out for adoption since it is neither fair nor right to place such a burden upon foster parents. Foundling homes, whether private or state, do not want them since they are a menace to the uninfected children. The problem of the care of such children will have to be solved by each state before long if the best interests of the people are to be safeguarded.

Turning now from the obstetric to the gynecologic side of the problem of syphilitic infection in women, we see even greater confusion and lack of accurate diagnosis. It has been seen how in women more than in men the external manifestations of the disease may be very slight and not revealed by the ordinary careful physical examination. This is true in gynecologic as well as obstetric patients, but the disease is more apt to be undiagnosed in the former class because childbirth must be considered in the past and not the present tense. We have seen how little light is thrown upon the problem by the most careful histories. Thus, the history of repeated miscarriages is not so conclusive or suggestive of syphilis as where the woman is giving or has just given birth to a macerated fetus.

Syphilis may give rise to organic lesions in any part of the female generative tract, just as any organ in the body may be similarly affected. It is a curious fact, however, that until recently very little attention has been given to local syphilitic changes in the female generative organs, exclusive of the parts that are open to inspection such as the vulva, vagina and cervix. A study of the literature, however, shows that observations regarding local syphilis in all parts of the female generative tract are accumulating so that before long we

shall be in a position to discuss intelligently a subject which has been neglected by the gynecologist up to the present time.

It is well to keep in mind two facts: (1) that many functional disturbances in women, supposedly due to derangements of the genital organs, may be due to an unsuspected luetic infection; (2) that gynecologic patients who fail to recover their health after operations upon the generative tract may be suffering from a serious general disease of far more importance than the local lesions for which the operations were performed. When the diagnosis of syphilis depended upon the results of physical examination combined with careful history of exposure and subsequent symptoms there was some excuse for the practitioner's failure to recognize the disease. There is no such excuse now that we can avail ourselves of the Wassermann test. Such tests will confirm our suspicions of luetic infection derived from histories of the cases and from physical examination, and reveal many unsuspected cases where the ordinary gynecologic treatment would have stopped short of a cure because the general disease would have been overlooked.

As in the case of the Obstetric Clinic, the proportion of syphilis in 216 gynecologic patients examined since the last report was much higher. In the first report the percentage was 5.6 while in the last series there were 28 patients with syphilis or 12.9 per cent, a figure more than twice as large as in the first series. Combining the patients in the two series we have 606 patients of whom 50 were syphilitic or 8.2 per cent. We were either more successful in our histories in the last series, or, perhaps, what is more likely, there was a larger proportion of wellmarked syphilis in the 28 women affected. More than half, 15 out of the 28, gave a definite history of the luetic infection, while from 13 no such history could be elicited.

In the first series only 5 out of 22 syphilitic women gave histories of infection. Combining the two series we find only 20 out of 50 luetic patients giving a history of infection. In many of the cases, both where there was a history of infection and where this was lacking, physical examination in the gynecologic clinic failed to arouse suspicion of the presence of syphilis. Additional evidence of lues was found by the syphilologist but that was to be expected. The point to be emphasized is that the same careful physical examinations have been made in this particular clinic for years with only an occasional patient suspected of being luetic. When, however, such examinations

are reinforced by routine Wassermann examinations, nearly 10 per cent of the patients are found syphilitic and are sent to the Department of Syphilology for a confirmatory diagnosis and treatment. This is due almost entirely to routine Wassermann examinations. Granted that in certain cases such examinations are unreliable, this is not true in the great majority of cases. So great a help has the Wassermann examination proved in the public clinic that arrangements are being made to have routine Wassermanns made on all patients in the private clinic. Hereafter such examinations will be as much a part of the regular preoperative routine as the careful examination of the urine. Only by such a routine will private patients receive treatment equal to that accorded patients whose financial circumstances are not as good.

This brings us finally to the consideration of how the practitioner can have routine Wassermanns made upon his patients. Such examinations are so technical that they must be made in special laboratories. If these laboratories are private, a fee commensurate with the importance of the examination must be exacted. The patient with suspicious signs of syphilis will pay such a fee, the ordinary patient will not, and after a few rebuffs the practitioner gives it up and routine Wassermanns are not made. Thus, a great deal of syphilis is never detected, or recognized too late for treatment to do the most good. Now syphilis is a contagious disease and it is of the utmost importance to the state that every case be diagnosed and properly treated. The state, county and townships do not hesitate to spend money in trying to prevent the spread of other contagious diseases. Why then should not the state support a laboratory where such examinations would be made for everyone, rich or poor, free of charge? To be sure the charge at the University serological laboratory is very small for patients outside of the hospital, but it is enough to prevent routine Wassermann examinations, and that is, after all, what is necessary if the unsuspected cases of this disease are to be discovered and patients given the best chance of recovery through appropriate treatment.

## RABELAIS' CONCEPTION OF SYPHILIS

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RABELAIS' opinion of syphilis is valuable because it undoubtedly includes views then held of this disease, given by a man with a genius for writing, who was at the same time a medical practitioner.

According to Felix Brémont there are considerably over eight hundred and fifty-two references to medical subjects in the four books of Rabelais.<sup>1</sup> The fifth book, probably as being apocryphal, is not included in this estimate. Of these references seventeen relate to syphilis. He, however, is accounted so little as a syphilographer that neither J. K. Proksch nor Iwan Bloch even mention him as such, and this for a cause. He was not a syphilographer.

While not underestimating the interest attaching to these references, one must never forget that Rabelais wrote, not for scientific purposes, but for literary effect, and that while he never seems to be able to avoid being a medical man, yet his principal theme is human nature and not natural history, such as the sciences involved in medicine really are. Furthermore he would have to depend almost entirely on his own observations for a knowledge of the disease, and he was not a scientific observer. He was a good observer and saw things in their correct light, and had a fund of common sense, and, of course, humor, but he had not a scientific training and he had not that store of exact observation at his hand that is so easily obtainable today. The only books on medicine that it is known he read contained no mention of syphilis. They were the Letters of Manardi, which he translated from Italian, and the Aphorisms of Hippocrates, which he translated from Greek, the works of Celsus, and some other Greek and Latin authors, none of which contained any mention of syphilis.

Rabelais probably began his medical studies while in Paris in 1528, when he was thirty-four years of age, and he died in 1553, aged

fifty-nine.<sup>2</sup> His active literary life falls well within a very productive period in the history of syphilis.

The literature of syphilis begins with Marcellus Cumanus, who was a physician in the Venetian army, fighting against Charles VIII, of France, in the war of 1494-5, and it was in this French army at the siege of Naples that syphilis, recently introduced from America, broke out as an epidemic. Cumanus noted his observations on the margins of his copy of Argelata's surgery, and from then on throughout the time that Rabelais lived many treatises were written on this disease, including the works of Torella, Villalobos, Pintor, Vigo, Ulrich von Hutten, Paracelsus, de Isla, and Lobera de Avila. Fra-castor wrote his celebrated poem from which we have the name, "Syphilis," and Guillaume Rondelet, who is generally accepted as the original of Dr. Rondibilis of Rabelais's works, also wrote a treatise on syphilis, entitled "*Liber de Morbo Italico*," which, however, was not published till 1560, seven years after Rabelais's death. Rabelais, therefore, lived at a time when the subject of syphilis excited the attention of many men, particularly in Spain and Italy, and some in France and Germany, but his own interest seems to have been a general one, and did not extend to the minute observation of facts, or to the details of caring for the sick, at least in this disease.

It was rather the forbidding crusted eruptions, the raucous voice, the misfortunes attendant on excessive treatment, the employment of the name of the disease in the mouth of the common people, for example as an imprecation, and the curious popular ideas in regard to the transmission of the malady that stirred in him the desire to write.

In the prologue to his first book, Rabelais dedicates his works to drinkers and to those who suffer from syphilis, and throughout his writings he repeatedly states that he only wrote to comfort and rejoice the sick. Gout and syphilis in Rabelais's day probably included the ailments of everyone who was chronically and miserably sick with the exception of those who were so evidently afflicted with leprosy that even the laity could recognize them as such.

There is no doubt Rabelais did not think that syphilis was introduced first into Europe by the returning sailors of Columbus, if he gave the matter a thought at all. He says that Gargantua's first teacher, the theologian, Master Thubal Holofernes, tutor of Gar-

gantua, died of the French pox in the year 1420, which would be seventy-two years before the discovery of America.<sup>3</sup> This date, however, as far as Rabelais is concerned, seems to have been a matter of little moment. His principal object was to introduce a rhyme taken from an epitaph that struck his fancy, and the date met the necessities of the rhyme.

#### LA VÉROLE

Rabelais, with one single exception, calls syphilis "*la vérole*," a corruption of a Latin word of the Middle Ages, *variola*, meaning a variegated disease, a disease of many phases. It was a term first applied to smallpox, and afterwards extended to include syphilis. It must not be supposed that because Rabelais calls syphilis by this name alone that it had not other designations. Knowledge of syphilis has often been scanty, but names for it have never been lacking, and Iwan Bloch says that within five years after Columbus's return from America all the chief appellations of syphilis were already given, and there were more than four hundred of them.<sup>4</sup>

Rabelais employs the term "*vérole*" in many ways; to designate the disease, as a simile of something neverfailing and ever present,<sup>5</sup> as a term of endearment,<sup>6</sup> as an imprecation, but to my knowledge he only uses it once as a malediction. In this passage he refers to "*Levitical hypocrites, swollen, pokified (véroles) and mangy, unquenchable in their thirst and insatiable in their eating.*"<sup>7</sup>

That Rabelais does not mention the name syphilis is not surprising. It is the name of one of the characters in a poem on that disease written by Geralamo Fracastoro [Fracastor], and published in Italy shortly before 1521. Rabelais may have been familiar with this poem as he visited Italy twice subsequent to this date, in the retinue of Cardinal du Bellay, in 1534 and again probably in 1535. The name syphilis had not then become vulgarized; I do not know that it was yet employed as a designation for the disease.

#### TRANSMISSION OF THE DISEASE

Rabelais knew that syphilis was transmissible, but the views expressed as to the manner of transmission are peculiar. He says that the first one who got the disease was Etion, one of the race of giants, and he acquired it because he did not drink new wine in summer time.<sup>8</sup> He also suggests how readily transmissible he considered it,

in relating that twenty-seven theologians of the Sorbonne got syphilis in passing by a trellis that Panurge had greased with a malodorous mixture.<sup>9</sup> This also indicates how the transmission of diseases and the presence of bad odors were associated in those days. Rabelais also mentions how a number of merry fellows made masks of the leaves of a holy book, the decretals, and thereby acquired syphilis and some other diseases.<sup>10</sup> The dominant idea here is evidently sacrilege as an etiological factor, and it is doubtful if the mediate transmission of the disease by the mask is intended.

In another passage he says that "the blessed fruit or seed of syphilis would immediately distil from the female genitalia like fine rain."<sup>11</sup> This is the nearest approach to the idea of a minute material infective agent that I have found.

In another place Rabelais points out the danger that an unmarried man runs of acquiring this infection. The rascally Panurge was wishful to get married and to enjoy the comforts of a quiet, domestic life, but like many lewd people, he had a grave suspicion of the virtue of any woman; his future wife, whoever she might be, included.<sup>12</sup>

A curious side light on Panurge's character is here given. Although he personally was cowardly, improvident, frivolous, and in every way most tricky, despicable and worthless, yet he knew the value of a virtuous woman, and he recognized how uniquely faithful the woman legitimately married shows herself as a nurse in illness. Some have said that Rabelais never practiced medicine—this alone would indicate that he had.

#### ERUPTIONS

Rabelais repeatedly refers to the crusted eruptions of syphilis. The ulcerated luetic lesions have a special inclination to form large thick crusts, constituting a diagnostic feature. These crusts are frequently dark brown or black from mixture with blood, and because of the spreading ulceration, repeated series of ever larger crusts are lifted up one on the back of the other immediately below it, forming a structure resembling an oyster shell, and now called rupia. These were named by Rabelais "croustelevez," literally "lifted up crusts." Croustelevez was a metaphor borrowed from the bakery, and originally meant the puffed up crusts of cooked bread. In one instance Rabelais calls the disease itself by this name.



## THE RAUCOUS VOICE OF SYPHILIS

Panurge, in pretending to have syphilis, writhed his mouth and twisted his fingers, and spoke with a hoarse voice.<sup>13</sup>

I well remember the first time I heard the raucous voice of syphilis. It was years ago while I was a student, and the coarse, rough, hollow sound grated so disagreeably on my ears that I have never forgotten it. This change from the beautiful tones of the human voice is something altogether repulsive.

Rabelais speaks of being syphilitic to the bone, "*verollez jusque à l'ous*," and he bids those who have the itch, and those who have syphilis to take their ulcers otherwheres, where they may get a good living, presumably by begging.<sup>14</sup> This way of turning infirmity to profit was particularly prevalent in the Middle Ages.

The expression "syphilitic to the bone" is probably a figure of speech, meaning "thoroughly syphilitic," and in a book like that of Rabelais, does not amount to a scientific statement of his knowledge of the existence of bone syphilis. The fact, however, that ulcers arose from syphilis was well known.

Rabelais refers to the sweat of syphilitics as being salty.<sup>15</sup> All sweat is, of course, salty, but tasting it may indicate a mode of examination prevalent in his day. Sweating the patient has always been a favorite mode of treating syphilis, and there is no doubt of its value as favoring elimination, and tasting the sweat might quite likely have been thought to furnish a sign of how the treatment was proceeding.

Examination of the secretions by tasting has not been, in the history of medicine, limited to tasting the perspiration.

## TREATMENT OF SYPHILIS

Rabelais describes how the visage of those who have syphilis and the gout shone when they were well anointed. Their teeth went rattling in their head like the keys of a musical instrument, and the foam arose in their throat as in a boar's, that the hounds had driven to bay.<sup>16</sup> This reference to the foam in the throat is particularly apt as it is one of the most tormenting incidents in salivation.

In a scene in hell a man who had occupied an exalted position on earth is described as being a mercurial rubber for those afflicted with syphilis. Epistemon, one of Pantagruel's retinue, who saw him

there, asked if then they had syphilis in hell. "Surely," he replied, "and more than one hundred millions of them." "And furthermore," he continued, "you may be certain that those who have not had syphilis in this world will get it in the next."<sup>17</sup>

The above shows clearly the mode of treatment, and that the patients were frequently salivated, that is to say, they were over-treated. The history of syphilis is a long history of over-treatment interspersed with intervals of what is worse, no treatment at all.

The study of Rabelais in regard to syphilis is profitable in many ways. Rabelais's dramatic talent was such that each man speaks of the disease in his own way. Rabelais himself mentions his precious syphilitic patients, and they are among the most grateful, uncomplaining patients a physician has. Friar John, the forthright speaker and hearty fighter, swears by syphilis, and it is one of the most picturesque oaths in his quite rich vocabulary. The cowardly, tricky Panurge fears syphilis, and this fear is so strong as to impel this vagabond to seriously consider contracting a legitimate marriage.

If there were no other evidence of the prevalence of syphilis in France in Rabelais' day, the familiar way the characters have of speaking of the disease in ordinary conversation would show it to have been so.

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<sup>3</sup>Gargantua, Chap. xiv.

<sup>4</sup>Der Ursprung der Syphilis von Dr. med. Iwan Bloch, 1901, S. 61.

<sup>5</sup>Pantagruel, Book ii, Chapt. xvii.

<sup>6</sup>Gargantua, Book i, Prologue de l'auteur, line 1.

<sup>7</sup>Prologue to Book iii.

<sup>8</sup>Pantagruel, Book ii, Chapt. i.

<sup>9</sup>Pantagruel, Book ii, Chapt. xvi.

<sup>10</sup>Pantagruel, Book iv, Chapt. lii.

<sup>11</sup>Pantagruel, Book ii, Chapt. xv.

<sup>12</sup>Pantagruel, Book iii, Chapt. ix.

<sup>13</sup>Pantagruel, Book ii, Chapt. xxix.

<sup>14</sup>Gargantua, Chapt. liv, line 50.

<sup>15</sup>Pantagruel, Book ii, Chapt. ii.

<sup>16</sup>Pantagruel, Book ii, Prologue.

<sup>17</sup>Pantagruel, Book ii, Chapt. xxx.

# Abstract of Current Syphilis Literature

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## History

**THE FREQUENCY OF HEREDITARY SYPHILIS.**—F. Churchill and R. S. Austin, Chicago. *American Journal of Diseases of Children*, 1916, vol. xii, p. 355.

The study of the literature on the incidence of hereditary syphilis shows a wide range of results, it being variously estimated at from 2 to 14 per cent in Europe and America. Intensive study of a group of 695 patients in the Children's Memorial Hospital during the winter 1915 and 1916, the study embracing both clinical and laboratory methods of investigation, shows an incidence of 3.3 per cent of hereditary syphilis. The amount of hereditary syphilis among hospital infants and children in four large cities of the United States—New York, St. Louis, San Francisco, and Chicago,—appears to range from 2 to 6 per cent.

## Etiology

**SPIROCHETE PALLIDA OR TREPONEMA PALLIDUM.**—William Allen Pusey, Chicago. *Journal of the American Medical Association*, 1916, vol. lxvii, 1621.

The commonly used name for the organism of syphilis is "Spirochete pallida." There is, however, a great deal of confusion as to whether that term is correct or whether the organism should be called the "Treponema pallidum." If the best usage means anything, spirochete pallida is an acceptable term for the organism of syphilis, and its almost universal use shows beyond question that the name has come to stay. A large number of authorities are quoted to sustain the writer's contention.

**SOME OBSERVATIONS ON THE TRANSMISSION OF SYPHILIS WITH PARTICULAR REFERENCE TO A PATERNAL SOURCE OF INFECTION.**—Udo J. Wile, Ann Arbor. *Journal of Cutaneous Diseases*, 1916, vol. xxxiv, p. 645.

Wile's observations have led him to believe that a paternal inheritance as outlined usually results in expulsion of fetus before birth in

the first pregnancies and stigmatized children, if such are born alive, in the late pregnancies. Maternal infection, therefore, would not be hereditary but would be an acquired form of syphilis except when syphilis is recent in the mother. For those cases in which maternal infection results in expulsion of the fetus, one would have to presume the infertilized ovum to be the seat of the resting or active stage of the spirochete as may occur with the male germ cell. That such is infrequent is established by the pathology of ovarian syphilis. Paternal infection, therefore, would be for most of the cases the commonest mode of transmission. With regard to the placental transmission, the weight of evidence is more in favor of a fetal infection of the placenta than of the infection of the placenta by the mother. The complement binding substance passing through readily from the fetus to the mother suggests an explanation for the uniformly positive tests in the mother and the otherwise inexplicable phenomenon that most of such mothers go through life Wassermann-positive without ever having clinical syphilis.

IMMUNITY IN SYPHILIS.—Hans Zinsser, New York. *Journal of Laboratory and Clinical Medicine*, 1916, vol. i, 785.

The syphilitic subject acquires definite resistance to reinoculation which becomes manifest soon after the appearance of the primary sore, at a time when the virus may be regarded as having gained universal systematic distribution. This resistance, high though not absolute, persists throughout the secondary or most active period of the disease and into the tertiary stage. During the latter, however, it appears somewhat to decline, reinoculation or superinfection being more frequently possible at this period. When syphilis is entirely cured, susceptibility may in all probability be regarded as returning, possibly, though not certainly, to the same degree as it exists in the normal subject. The reasons for this last belief will become more clear when we study the evidence contributed by animal experimentation.

SYPHILIS WITHOUT CHANCRE IN WOMEN.—Gaucher. *Bulletin de l'Académie de Médecine*, 1916, vol. lxxvi, p. 259.

Four cases are described in which syphilis occurred without chancre. In one case the infection followed a laparotomy in which the assisting surgeon had mucous patches in the mouth. The same etiology is suspected in a second case. Another case occurred in the person of a surgeon who cut his finger during an operation on a syphilitic. The fourth case was due to an injection made with the same needle that had just been used on a syphilitic in whom the disease had not been diagnosed. Ten cases are mentioned in which it seems certain that women had been inoculated in the uterine mucosa by infected semen independent of pregnancy.

## Pathology

THE PERSISTENCE OF ACTIVE LESIONS AND SPIROCHETES IN THE TISSUES OF CLINICALLY INACTIVE OR "CURED" SYPHILIS.—A. S. Warthin, Ann Arbor. American Journal of the Medical Sciences, 1916, vol. clii, p. 508.

Warthin is very pessimistic as to the curative effects of many of the present day methods of treating syphilis and urges that our conception of syphilis, both pathologically and clinically, must be reshaped in the light of the spirochete.

In the pathological service in the University of Michigan there were from 1912 to 1914, 41 autopsy cases that on a microscopical examination showed active syphilis determined either by the presence of the spirochetes or by characteristic lesions. Of these there were 11 cases with a clinical diagnosis of recognized and treated syphilis regarded clinically as cured, 5 cases of active syphilis under treatment for symptoms of the disease, and 25 cases in which a diagnosis of syphilitic infection was excluded clinically because of the absence of symptoms and denial of previous infection. In all of these 41 cases the lesions of active syphilis were practically of the same nature whether in cases that had been treated or were being actively treated, or had received no treatment at all. Active syphilitic lesions were found in the heart in 36 cases, in the aorta in 32, in the testes in 31, in the liver in 4, in the adrenals in 6, in the spleen in one case, pancreas in 6 cases, and central nervous system in 5 cases. As 5 of the cases were women and deducting these, the lesions in the testes occurred as frequently as those in the heart. The organs most frequently the seat of active lesions, in order of frequency of occurrence, would be the aorta, heart, testes, adrenals, pancreas, central nervous system, liver and spleen.

It is also of great interest to know that in these cases there were 16 cases of subacute or chronic parenchymatous nephritis; 20 acute parenchymatous and 5 cases of interstitial nephritis although no relationship between the syphilitic and the kidney lesions can be positively affirmed. In the determination of the existence of syphilitic infection in many given cases coming to autopsy, the heart, aorta, and testes in the male are the organs that should receive the most thorough examination.

Warthin believes that the heart and aorta of every latent syphilitic are involved in the infection and that from the standpoint of life insurance, latent syphilis becomes a medical and sociological factor of the greatest importance.

Our present day treatment seems only to succeed in rendering the infection latent rather than curing it. Clinical cures may not be cures at all as shown by the autopsy. From the standpoint of eugenics it may also be said that absolutely all symptoms or even all history of infection and a negative Wassermann reaction cannot be taken as an absolute criterion of freedom from latent syphilis.

### Symptomatology

**A STUDY OF THE INVOLVEMENT OF THE BONES AND JOINTS IN EARLY SYPHILIS.**—U. J. Wile and F. E. Seneac, Ann Arbor. *American Journal of the Medical Sciences*, November, 1916.

One hundred and sixty-five cases of syphilis in the primary and secondary periods have been studied during the past two years with particular reference to early bone and joint involvement. In all cases the long bones were carefully palpated and percussed for tenderness. A careful note was made on the subjective symptoms pertaining to the bone and joint involvement, and all of the joints were carefully examined for objective lesions and functional impairment. In a few cases, in which objective pathology was noted, the roentgen ray was also used.

In all, sixty cases of the one hundred and sixty-five were found to have symptoms or objective findings referable to the pathology of the osseous system. Of the sixty cases in which the bones and joints were involved, sixty per cent of the skeletal involvement was found associated with general health disturbance. All types of syphilides in about an equal proportion were found to exist with the bone manifestation.

Forty-five per cent of the cases in which bone and joint involvement was present were cases also of neural syphilis. In about thirty per cent of those cases in which the bones and joints were involved definite splenic enlargement could be demonstrated.

In all but one case in which the bones were involved more or less pain was present. For the most part the pain was nocturnal and was relieved somewhat by exercise.

Arthralgia was the most common finding referable to the articulations. It was present in seventeen of twenty-one cases examined. In the order of frequency the ankles, the metatarsophalangeal joints, and the elbows were affected and in one case the elbow and shoulder joint of the same side were affected. Pressure on such joints was always followed by sharp pain.

The authors conclude that the skeletal structures offer no exception to objective or subjective involvement in early syphilis. The apparent and relative infrequency of their occurrence is easily found in the fact that ambulatory cases of syphilis are seldom examined with regard to the bony structure.

The frequent association of the osseous system with the involvement of all other systems would seem to indicate that there is no justification for assuming an osteotropic strain of the infecting organisms.

**SYPHILIS AND TRAUMA.**—W. P. Coues, Boston. *Interstate Medical Journal*, August, 1916.

Syphilis may at times cause brittle bones, and lead to fractures from traumatism which would, in a person free from syphilis, not

lead to fracture. All cases of fracture with long delayed or fibrous union should be searchingly examined for possible syphilis. Such patients usually present no outward easily recognized symptoms of the disease. This examination should include a Wassermann test on the blood and a radiographic study of other bones of the body. The tibia, fibula, radius and ulna, clavicle, and bones of the hands should be studied.

In wounds of the soft parts either surgical or traumatic, ulceration, without frank sepsis and constitutional symptoms, should arouse our suspicions even if the character of the ulceration is not frankly specific.

Internal trauma (railroad accidents, falls, and blows where the symptoms keep up without definite findings for long periods) should be viewed with suspicion. Skeletal manifestations of old syphilis may be found in these cases through radiography and other modern means of diagnosis at our disposal.

**THE COINCIDENCE OF LATENT SYPHILIS AND DIABETES.**—A. S. Warthin and U. F. Wilson, Ann Arbor. *American Journal of the Medical Sciences*, August, 1916.

Since 1907 there have occurred in the autopsy service of the pathological laboratories in the University of Michigan six autopsies on cases of diabetes mellitus. All six of these cases presented histological changes of syphilis the spirochetes being demonstrated in the myocardium in four cases and in one of these cases also in the pancreatic lesions. The diagnosis of syphilis in these cases of diabetes was made upon histological changes alone in two cases and in the remaining four cases upon both the histological changes and the presence of spirochetes in the tissues.

The material shows that a combined interlobular and interacinar type of pancreatitis with the loss of the islands of Langerhans is frequently associated with old latent syphilis.

In the great majority of cases the pancreatitis is localized and patchy in character and more rarely severe and diffuse. Diabetes may be associated with the more marked degrees of the syphilitic pancreatitis and in the autopsy service of the authors all their diabetes cases have been so associated, but a number of cases of syphilitic pancreatitis of similar degrees of severity have not presented the clinical symptoms of diabetes. It seems very probable, therefore, that latent syphilis is the chief factor in the production of the form of pancreatitis more frequently associated with diabetes, but that diabetes is not always coincident with severe degrees of this type of pancreatitis.

ADDISON'S DISEASE OF SYPHILITIC ORIGIN.—Phillip M. Schaffner and Tasker Howard, New York. *New York Medical Journal*, 1916, vol. ciii, p. 1026.

A search through 12 text books on syphilis discloses the fact that two state that Addison's disease may be of syphilitic origin and that one text book reports two cases. The authors report a case in a man of 38 who was troubled two years ago with a loose cough and an attack of vomiting. Later he suffered from a sensation of numbness in his hands and feet. Shortly after this he noted that his skin was becoming dark, this was particularly noticeable on the forehead, neck, axillæ, antecubital, inguinal and popliteal fossæ and the waist line. The lungs showed signs suggesting tubercular infection of both apices. The blood pressure was 98 systolic and 80 diastolic, his sputum contained no tubercle bacilli, the Wassermann was a double plus. The patient was immediately placed upon antisyphilitic treatment consisting of salvarsan and mercury. He responded immediately to the specific treatment and improved steadily. He has gained 19 pounds in weight and his wife states that his color is lighter than she has ever known it to be.

TESTICULAR SYPHILIS.—M. Zigler, New York. *New York Medical Journal*, 1916, vol. civ, p. 998.

Since almost 40 per cent of adult syphilitic males eventually acquire syphilis of the testicles, it behooves us to be more on the watch for chronic interstitial orchitis. Mistakes in the diagnosis in syphilis are so numerous that we must consider the possibility of syphilis in almost every patient who comes to us, no matter what the complaint.

Zigler reports three cases of testicular syphilis two of which were gummatous, one of which was absolutely unsexed and the other partially so. Two of the patients did not know that they had been infected with syphilis.

SYPHILITIC EPIDIDYMITIS.—F. R. Wright, Minneapolis. *The Urologic and Cutaneous Review*, 1916, vol. xx, p. 661.

Wright reports two cases of this condition both of which are old cases. In the first there is no history of infection. The patient has been married six years. His wife has never become infected and she has two healthy children, the oldest of whom is five years. In the second case there is the direct history of a sore 15 years ago which persisted for six weeks. This case is accompanied by a typical syphilis of the prostate, that is, a moderate, elastic enlargement with excessive tenderness and pain. There is no tendency to formation of gummata in either of these cases as is said to be the typical lesion in the late cases. The testicles in both cases are normal.



SYPHILIS OF THE BODY OF THE UTERUS.—Charles C. Norris, Philadelphia. *Surgery, Gynecology and Obstetrics*, 1916, vol. xxiii, 268.

Very little is said in the literature upon syphilis of the body of the uterus, but this organ is not immune to the ravages of this disease. Gummata have been found in the uterus particularly in the endometrium. A more common form of syphilitic endometritis manifests itself by changes in the glands and stroma, the latter being chiefly involved. It is characterized by changes in the blood vessel walls and condensation of the stroma. Ulceration of the endometrium is not infrequent, particularly during the tertiary stage. Lesions of the myometrium may be divided into (1) a more or less diffuse metritis which is usually accompanied by inflammation of the endometrium and (2) gummata. In the former condition the uterus retains its normal shape, it may or may not be enlarged and is usually harder and firmer than normal.

Gummata of the uterus may be single or multiple and vary considerably in size but are usually moderate in dimension, and differ in no respect from similar lesions arising elsewhere in the body. Hemorrhage is the symptom which has attracted the most attention, its most frequent form being menorrhagia.

The author reports one case of syphilis of the uterus. This patient contracted syphilis six years ago, antisyphilitic treatment was discontinued 9 months ago. Menorrhagia and other symptoms of syphilis of the body of the uterus developed three months later. The Wassermann test at this time was strongly positive. The chief pathologic lesion was the great softening and friability of the uterus together with the more typical changes usually produced by syphilis.

OBSERVATIONS ON THE OCCURRENCE OF SYPHILIS IN THE UNIVERSITY OF MICHIGAN OBSTETRIC AND GYNECOLOGIC CLINIC.—Reuben Peterson, Ann Arbor, *Surgery, Gynecology and Obstetrics*, 1916, vol. xxiii, p. 280.

In 2000 patients there were 110 distinctly positive Wassermans. Among the doubtful reactions there were 8 in which the patients were afterward proved to be syphilitic. This shows that practically six per cent of the general run of hospital patients are syphilitic. The percentage varied in the different departments as follows: Obstetrics and gynecology, 4.8 per cent; medicine, 4.7; ophthalmology, 8.7; otolaryngology 5.0; general surgery, orthopedics, and genito-urinary, 4.1; pediatrics, 11.0.

The percentage of lues in 381 cases in the University Maternity was 4.7 as shown by the Wassermann reaction and expert physical examination. In 18 cases of syphilis among the number examined only 8 gave a history of lues. In only 5 of the 22luetie patients in the gynecological clinic was there a history of syphilis.

**TWO CASES OF SYPHILIS OF THE LUNG.**—Abner Post, Boston. *Boston Medical and Surgical Journal*, 1916, vol. clxxiv, p. 876.

Two cases of syphilis of the lung are reported and radiographic pictures are shown. The resemblance of the pictures in the two cases is very striking. In both the dark shadow is confined to one side; in both the heart is drawn toward the affected side. Both patients were syphilitic, and in neither were tubercle bacilli found.

Diseases of the lung in which consolidation is found in unusual positions, or limited entirely to one lung, in which tubercle bacilli have not been found, may be considered suspicious of syphilis. If the Wassermann is positive the suspicion is much greater, and may almost be regarded as a certainty. Certainly consolidation in unusual positions with the absence of tubercle bacilli and the presence of a positive Wassermann does not permit the diagnosis of tuberculosis. The cases show also the very important fact that syphilis of the lung occurs in hereditary cases, that is, the young, the very individuals who are most subject to tuberculosis.

**SYPHILIS OF THE BLADDER.**—James Pedersen, New York. *Medical Record*, 1916, vol. xc, p. 235.

After a review of the literature and the reports of five new cases the author concludes: (1) Syphilis of the bladder is an entity often overlooked or not recognized. (2) It may manifest itself in one or more of several possible pathologic lesions only one of which, the punctate hyperemia in multiple spots, the so-called macule, is pathognomonic. (3) The other lesions having the same general appearance of benign or nonmalignant lesions not due to syphilis cannot be differentiated cystoscopically; some corroboration is necessary for diagnosis. (4) Suspected, recognized and treated, the prognosis seems uniformly good.

**LUES MALIGNA WITH REPORT OF TWO CASES.**—Perry A. Bly, Rochester, New York. *Journal of the American Medical Association*, 1916, vol. lxxvii, p. 508.

The histories of two patients with lues maligna are reported which offer several interesting features. Each fulfills the requirements of the definition of lues maligna; the great destruction of tissue with symptoms of a toxemia and the total absence of response to anti-syphilitic medication however vigorously employed. In each there was a long period of apparently good health followed by a rapid development of late syphilitic manifestations. In each case the tonsil was the starting point of the illness and of necrotic process. In each the severe systemic distribution and the rapid destruction of the tissues were preceded by traumatism to the tonsil or peritonsillar structures: in one case mechanically by tonsillectomy, in the other case by the application of caustic.

**SYPHILIS OF THE STOMACH; A CASE OF HOUR-GLASS CONTRACTION.—**

R. M. Culler, Hot Springs, Arkansas. *Journal of American Medical Association*, 1916, vol. lxxvii, p. 1667.

This case has some peculiar features which illustrate with what perfection syphilis may masquerade as some other disease. The patient was a man of 44, who contracted a sore in 1898. There were no symptoms referable to the initial lesion until 1908 when a lump appeared upon the shin following a slight injury. This was diagnosed syphilis and was treated for one month. Several years later a severe iritis arose; shortly after recovery from this he began to have "stomach trouble" consisting of indigestion, vomiting, and pain and tenderness in the epigastrium. Several physicians pronounced his case one of gastric ulcer. Operation showed a very hard and dense prepyloric hour-glass contraction. A partial gastrectomy was done and recovery was uninterrupted.

**CLINICAL SIGNS AND DIAGNOSIS OF LATE HEREDITARY SYPHILIS.—**

P. C. Jeans, St. Louis. *American Journal of Diseases of Children*, 1916, vol. xii, p. 374.

The Wassermann reaction is positive in practically 100 per cent of late cases in childhood. The value of the family history needs no emphasis.

Among the author's cases the father gave a positive reaction in less than 50 per cent of those tested even though he was the starting point for the infection in the family. The mother's reaction is positive more frequently. Rhagades are pathognomonic, to be characteristic, however, they must be definitely linear and not confined to the angle of the mouth.

From the standpoint of frequency Hutchinson's teeth is not a valuable sign though when present constitutes good, but not absolute evidence of an early infection.

Cranial bone disease other than rickets is rarely due to anything else than syphilis and usually leaves some deformity.

Corneal opacities, though in no way a proof of syphilis are helpful in connection with the history.

Deafness, without obvious destruction of the ear, complete in the course of a few weeks is almost pathognomonic of syphilis.

Scaphoid scapulæ, though suggestive have not proved more useful than other disturbances of development.

Rheumatic pains which may be periosteal, bone, muscle, or nerve root pains are important from the viewpoint of diagnosis because they yield so readily to proper treatment.

**CONJUGAL PARESIS.—**

H. H. Drysdale, Cleveland. *Journal of the American Medical Association*, July 29, 1916.

Drysdale reports a case of conjugal paresis which presents some very interesting features: the father and mother are now hopelessly

paretic as the result of the ravages of syphilis. Their only daughter has inherited the disease. The husband contracted syphilis two years prior to his marriage, the symptoms were slight and quickly subsided after a brief period of treatment. Eighteen years preceded the development of paresis in his case. Unquestionably he infected his wife, but just when no one can say. She did, however, become a paretic two years after her husband, who was syphilitic two years before they were married. It will be interesting in this connection to know if the number of years of syphilis preceding the appearance of paresis were the same in husband and wife. The disease in both cases was of the demential type.

CARDIAC CRISES IN TABES DORSALIS—REPORT OF A CASE WITH SUDDEN DEATH.—M. F. Lautman, Hot Springs, Arkansas. Medical Record, October 21, 1916.

Attacks of pain about the heart in tabes are not uncommon. True cardiac crises, however, are extremely uncommon, in fact their existence, as a manifestation of tabes is a matter of dispute. The case reported occurred in a man 46 years old, who had an initial lesion followed by a rash 20 years ago. For the past 8 months he had attacks of pain over the heart. These pains come on quite suddenly, are stabbing in character, and radiate up into the neck. The pain is very severe while it lasts, the heart seems to stop beating, but the attack usually disappears about five minutes after reaching its maximum intensity. There were no postmortem evidences to explain the sudden death which occurred in one of the paroxysms, which renders quite plausible the assumption that death was due to a cardiac crisis.

HEREDITARY SYPHILIS IN THE LIGHT OF RECENT CLINICAL STUDIES.—Borden S. Veeder, St. Louis. American Journal of the Medical Sciences, 1916, vol. clii, p. 522.

Although, in all probability, germinal transmission does not occur, it has been found that the seminal fluid can give the infection and the testicles are recognized as a not infrequent seat of latent syphilis.

In a recent study of familial syphilis made in this clinic in St. Louis the blood of 85 mothers of syphilitic children was tested. Seventy-four of these mothers denied all knowledge of infection nor was there anything in the history which would indicate syphilis other than a history of frequent abortions. Of these 85 women, 73 gave a positive Wassermann reaction. In this way, by means of the Wassermann test, it has been found presumable that these apparently healthy mothers are immune in Colles's sense because they have syphilis in the latent form.

In a study of 100 syphilitic families, 331 pregnancies occurred which resulted as follows: abortions 100, or 30.2 per cent; stillbirths

31, or 9.3 per cent; living births 200, or 60.5 per cent. Considering the 200 living births, at the time the data was collected 39 were dead and 161 alive, but 12 of the 161 died during the course of the investigation. Of the 161 examined, 107 had both clinical symptoms of syphilis and positive Wassermanns; 5 were clinically positive but gave negative tests; 16 were clinically negative and gave positive reactions. Thus but 33 of the 161 living children were free from the infection.

Positive reactions in nonsyphilitic patients are extremely rare and in all of the patients with the late type there were 90 per cent with the infantile type of hereditary syphilis. The Wassermann reaction in untreated cases was positive.

Veeder's experiments with the luetin test are very limited but he believes that it cannot offer any advantages over the Wassermann reaction in the determination of hereditary syphilis.

We are accustomed to regard hereditary syphilis as a disease particularly amenable to treatment. If we judge the results of treatment by its immediate effects upon the clinical symptoms this holds true, but it is not true when we consider treatment in its relations to the ultimate cure of the disease.

It is extremely difficult to obtain a persistently negative Wassermann reaction as the result of treatment and particularly so in the late cases.

Neosalvarsan is the drug of choice to make an acute lesion disappear in the shortest time, but for the long continued treatment, which is necessary, mercury is preferable, gray powder being the most satisfactory form.

A STUDY OF PROXIMO and ACRO-ATAXIA IN TABES DORSALIS.—Frederick B. Clarke, Milwaukee. *American Journal of the Medical Sciences*, 1916, vol. clii, p. 574.

Clarke states that inasmuch as Hoover claims that in tabes dorsalis ataxia of the proximal extremities of the limb occurred earlier and could be demonstrated before acro-ataxia or ataxia of the distal portion of the limb, 10 cases were selected for study which were, with one exception, in the preataxic stage.

He concludes that in tabes there is a more frequent and more marked ataxia in the distal than in the proximal articulations of the limb and that the distribution of the ataxia cannot be used clinically as a means to differentiate tabes dorsalis from the subacute combined degeneration of the cord which occurs in some cases of pernicious anemia.

SYPHILITIC PSYCHOSES ASSOCIATED WITH MANIC DEPRESSIVE SYMPTOMS AND COURSE.—Albert M. Barrett, Ann Arbor. *Journal of the American Medical Association*, 1916, vol. lxvii, p. 1639.

Nine cases are reported illustrative of this type of case showing a certain recurrence of attacks. This emphasizes the resemblance to

maniae depressive insanity. In all of these cases there were mental symptoms which differ much from the usual clinical picture of general paralysis and seemingly are unrelated to the direct effect of a syphilitic process involving the brain structure.

It seems justifiable to regard cases of this type as coincidental occurrences of maniac depressive types of reaction and syphilitic disease of the type of general paralysis.

### Diagnosis

THE DIAGNOSIS AND GENERAL TREATMENT OF SYPHILIS.—J. A. Fordyce, New York. *American Journal of the Medical Sciences*, October, 1916.

The fate of the syphilitic individual depends upon the early diagnosis of his infection and the intensity with which treatment is carried out in the first six months.

The dark-field illumination should be employed in every case of chaneroid to confirm or rule out the possibility of coincident infection with the spirochetes. The Wassermann test is of special value in all conditions of obscure etiology referable to the cardiovascular system, cerebrospinal system, or viscera in which syphilis might be a factor and in cases with a definite clinical picture.

The examination of the spinal fluid enables us to determine the activity of the luetic process in the brain or cord to distinguish the various pathological types affecting the central nervous system and in many cases to differentiate these and nonsyphilitic infections.

An analysis of the spinal fluid is not complete unless the Lange or colloidal gold test is performed in addition to the Wassermann reaction and a cytological and chemical examination.

In primary syphilis where the spirochetes are demonstrated and the Wassermann reaction is negative it is possible to cure syphilis with salvarsan alone. It is better to give six to ten doses and follow this with mercury for perhaps six months.

In secondary syphilis when the early rash is present and the Wassermann positive it is better to precede the salvarsan with several injections of a mercurial salt preferably a soluble one. After the salvarsan is begun the treatment is to be continued with mercury.

The possibility of involvement of the nervous system in secondary syphilis should be borne in mind. The most frequent evidences are irregularity of the pupils, persistent headache, and optic neuritis or auditory disturbances.

In latent syphilis with a positive Wassermann an investigation should be made of the cardiovascular and nervous systems or of previous involvement of any of the viscera, as for instance hepatitis.

In cardiovascular syphilis a prolonged use of mercury in connection with potassium iodide is perhaps of more value than the haphazard use of occasional doses of salvarsan.

In bone and periosteal lesions attended by severe pain there is no

drug in the pharmacopœia that produces so rapid an effect in relieving the pain and reducing the neoplasm as potassium iodide.

The criteria of cure are a negative Wassermann for at least a year continuing so after a provocative injection of salvarsan and a normal spinal fluid.

ATYPICAL PRIMARY LESIONS IN THE EARLY DIAGNOSIS OF SYPHILIS.—

John H. Stokes, Chicago. Interstate Medical Journal, August, 1916.

In genital lesions, it is conservative to regard every postcoital lesion as worthy of sufficiently prolonged observation (until after the possibility of secondary eruption is passed), to establish the absence of syphilis, and every chaneroid as a possible *ulcus mixte*.

The investigation of such lesions demands (a) an *untreated* lesion; (b) repeated dark field examinations of the secretions; (c) aspiration of the base of the lesion if indurated, and of adjacent glands; (d) repeated Wassermann tests, at least on the fourth week and the second and third months after the appearance of the lesion.

In extragenital lesions, persistence, adenopathy and failure to demonstrate frank epithelioma microscopically are grounds for suspicion, and should be ingrained into the mind of every physician, to apply under all circumstances. The dark field is a *sine qua non* in the early identification of this type of lesion.

The referring of cases, or of lymph from lesions, anaerobically preserved in sealed capillary tubes, to nearby experts for dark field search should be resorted to by the physician who is not in position to do the work himself.

The hot bichloride soaking in the local treatment of lesions, as described, is of value in making possible the recognition of suspicious induration developing under a healing chaneroid.

*Syphilis d'emblee* may be simply a confession of failure to find the chancre. Examination of the urethra in doubtful cases is indicated.

Abortive antisiphilitic treatment for doubtful cases where the risk of transmission of the infection is great, as suggested by Neisser, is worthy of discussion.

Even the most painstaking examination may fail to demonstrate the primary focus, apparently, so that in the last analysis no case should be dismissed with negative findings until a sufficient period of observation and study has eliminated the last possibility of error.

SYPHILITIC FEVER IN RELATION TO GYNECOLOGICAL AND OBSTETRICAL PRACTICE.—Fred J. Taussig, St. Louis. Surgery Gynecology and Obstetrics, 1916, vol. xxiii, p. 274.

The diagnosis of syphilitic fever can rarely be made with absolute certainty, but we should more often consider it as a possibility and institute antiluetic measures in suitable cases.

Secondary syphilitic fever occurs in a mild form in 20 per cent

of patients at the outbreak of the rash and at all times is prolonged and more severe in its course. Late secondary syphilitic fever is occasionally seen in a pronounced form after confinement or in gynecological patients.

Tertiary syphilitic fever is practically never due to syphilitic lesions in the female genital tract. One such case is reported by the author. It may, however, complicate a gynecologic or obstetric condition, and, owing to the difficulty in locating the site of tertiary lesions, lead to a wrong diagnosis as to the cause of the fever. All doubtful cases should be subjected to a Wassermann test, and, if positive, given antiluetic treatment.

Syphilitic fever is probably due to the reaction of the body to the toxins produced by the spirochetes, which under certain circumstances, or in certain individuals, gain an entrance into the circulation.

**CERTAIN PHASES OF SYPHILIS IN THE NEGRO FEMALE FROM THE STAND-POINT OF MEDICAL DIAGNOSIS.**—S. C. Jamison, New Orleans. *New Orleans Medical and Surgical Journal*, 1916, vol. lxix, p. 96.

These observations are based on the cases of syphilis diagnosed in the examination of 1000 consecutive medical cases in the clinic of the Charity Hospital. There were 166 cases diagnosed as syphilis, or 16.6 per cent.

We frequently hear the loose statement among doctors that there is 60 per cent or more of syphilis among the negro population. From the standpoint of internal medicine this is entirely unfounded so far as the negro female is concerned. On the other hand, syphilis, in point of numbers, heads the list of diseases in these 1000 cases, there being three times as many cases of syphilis as of tuberculosis, which is next in point of number, and over 20 times as much syphilis as malaria. Although 25 per cent of these cases have had vaginal examination it has been very rare that the chancre or its scar has been demonstrated. The rarity of skin lesions in these cases has been surprising; on the other hand, mucous patches are common. Gummata, especially of the periosteum, have been fairly common.

The incidence of syphilitic arthritis is very high among the negro females. Pain, worse at night, is easily the most common symptom that these cases have presented. The history of repeated miscarriages, with negative pelvic examination, is exceedingly common and significant. The serum reactions have been performed 81 times on the 166 cases diagnosed as syphilis, which were positive 65 times and negative 16 times. In these 1000 cases not a single case of aneurysm was diagnosed and it is believed that it is rare in the negro female, though its prevalence in the negro male is so great.

Again in contradistinction to the male, there have been only two cases of aortic regurgitation; there have been two cases of tabes, and one of paresis.



THE WASSERMANN REACTION IN ITS RELATION TO TUBERCULOSIS.—Captain C. G. Snow and Captain A. F. Cooper, Medical Corps, United States Army. *American Journal of the Medical Sciences*, August, 1916.

This study was begun with the object of ascertaining the number of patients in the United States Army General Hospital, Fort Bayard, New Mexico, who might give a positive Wassermann test in the presence or absence of syphilis, most of the patients being tuberculous. The experiment seems to prove that tuberculosis might not in the absence of syphilis present a positive Wassermann reaction but that it does so under certain circumstances.

Careful titration, accurate dosage and unlimited trouble are necessary to eliminate error. The following conclusions are drawn: (1) That the percentage of nonsyphilitic tuberculous patients, whose blood may bind complement with noncholesterinized antigen, is so small as to be practically negligible. Complete complement fixation with noncholesterinized antigen in a tuberculous patient is as adequate presumptive evidence of syphilis as it is in a nontuberculous. (2) That the sera of nonsyphilitic tuberculous patients may give a partial plus minus to complete double plus complement fixation with cholesterinized antigen in about 31 per cent of cases.

THE MARGIN OF ERROR IN THE WASSERMANN REACTION.—Irving Simons, R. L. Jones, and W. B. Goddard, Nashville, Tennessee. *Interstate Medical Journal*, August, 1916.

These investigations were based upon a series of one thousand Wassermann reactions done upon specimens of blood, divided in two or more portions, kept under approximately the same conditions and tested by two or more laboratories. The tabulated reports seem to merit the following conclusions:

1. The results in the Wassermann reactions carefully given out with proper technic by two laboratories should yield a very high percentage of agreement. In this series this reached 93.5 per cent in one thousand tests.

2. The index of error while not negligible, would appear to be small. In this series it amounted to 6.5 per cent in one thousand tests.

3. Some of this error is due to the difficulty in the standardization of the sheep's blood, the complement, and the amboceptor, inasmuch as higher results were obtained when both laboratories used the same reagents.

4. More of this error was eliminated when in addition to this the same antigen was used by both laboratories.

5. It is believed advisable that two or more specimens of Noguchi's acetone insoluble fraction antigen be used in the Wassermann reaction.

THE RELATION OF THE LUETIN SKIN REACTION TO IMMUNITY IN SYPHILIS.—John A. Kolmer and Stuart Broadwell, Jr., Philadelphia. American Journal of Immunology, August, 1916.

As a part of a series of studies bearing upon the question of anaphylactic skin reactions in relation to immunity the luetin test was performed on a large series of persons, mainly those in the tertiary and latent stages of syphilis and showing involvement of the tissues of the central nervous system.

The sera of a large number of these persons yielding typical luetin reactions of varying degrees of severity; also the sera of syphilitic persons yielding negative luetin reactions, and the sera of normal nonsyphilitic persons were tested for treponemicidal activity *in vitro* and also for agglutinin and complement-fixing power in order to determine the relation, if any, between the occurrence of the anaphylactic skin reaction and the presence or absence of these antibodies.

The results of this study conducted with one culture of *Treponema pallidum* may be summarized as follows:

1. Fresh active normal serum exerts no treponemicidal action on culture pallida *in vitro* in the proportion of one or two parts of serum to one part of diluted fluid culture.

2. The sera of persons in the tertiary and latent stages of syphilis exert no appreciable treponemicidal action on culture pallida *in vitro* under similar conditions.

3. The sera of syphilitic persons yielding typical luetin reactions did not exert any treponemicidal activity *in vitro*.

4. There is no direct relation between the occurrence of cutaneous hypersensitiveness to luetin and the presence of agglutinin for culture pallida in the blood serum.

5. There is no direct relation between the occurrence of cutaneous hypersensitiveness to luetin and the presence of complement fixing antibody with an antigen of luetin in the blood serum; both the anaphylactic and complement-fixing antibodies were present or absent together in 52 per cent of cases, while the former was present and the latter absent in 40 per cent. The anaphylactic and complement-fixation reactions indicate an infection with *Treponema pallidum*, but as based upon experiments *in vitro* neither can be regarded as indicating the co-existence of a treponemolysin or as an index of immunity to syphilis.

6. The sera of a larger percentage of syphilitics contain agglutinin for *Treponema pallidum* than complement-fixing antibody when luetin is used as antigen. It is probable that this difference is due in large part to the poor antigenic sensitiveness of luetin as antigen; when ordinary lipoidal extracts were used as antigens both complement-fixation and agglutination occurred together with the majority of sera.

7. As based mainly upon the results of these treponemicidal and

other tests *in vitro*, the anaphylactic luetin test cannot be regarded as an index of resistance to *Treponema pallidum*; these experiments and the failure of others (Neisser and Bruck; Nakano and Noguchi) to produce active immunity to syphilis in animals indicate that a lytic type of immunity is absent in syphilis or, at least, that it plays but a minor role in this infection.

THE WASSERMANN REACTION IN GYNECOLOGY.—Philip F. Williams and John A. Kolmer, Philadelphia. *American Journal of Obstetrics and Diseases of Women and Children*, 1916, vol. lxxiv, No. 4.

With the view of ascertaining to what extent unsuspected syphilis is present and of determining what significance a positive reaction might have in gynecology, a Wassermann test has been made upon the blood of three hundred cases, such as might be made in the average gynecological dispensary and ward service, no selection being made as to the type of lesion present. The percentage of positive reactions, 22.6, corresponds closely with the generally accepted incidence of syphilis in adults. This incidence of syphilis in gynecology on the basis of the Wassermann reaction is so definite that this disease cannot be excluded on the basis of a negative history and the absence of demonstrable evidence of syphilis; while a particular lesion may not be syphilitic, it is, however, highly important to institute antiluetic treatment if syphilis is demonstrated by the Wassermann test.

Of particular interest is the relatively high percentage of positive reactions observed in the following conditions: stillbirths, 75 per cent; rectal diseases, 50 per cent; amenorrhea, 50 per cent; habitual abortion, 50 per cent; pelvic inflammatory disease, 36 per cent; sterility, 33 per cent; abortion and miscarriage, 29 per cent; metrorrhagia, 20 per cent; myomata of the uterus, 16 per cent, gonorrheal vaginitis, 10 per cent; pregnancy, 17 per cent.

The social condition has played no part in increasing the percentage of positive reactions in this series; some of the single women were parous, and a number of the married women were sterile. Race, however, seems to be a more important factor, 35.8 per cent of the black race gave positive reactions as compared with 20.2 per cent in the white women. The history of infection has been obtained in but a few cases. This is a well-known fact, it is not the intent of the patient to deceive, but the primary lesion in women is overlooked and the secondary stage may have been disregarded.

The high degree of latent syphilis in women should make a routine Wassermann test in gynecological and obstetrical practice as advisable as any other laboratory procedure; it is certainly as advisable here as in medical and surgical practice.

The Wassermann reaction under proper conditions has proved highly specific and an indispensable diagnostic aid. Particularly dur-

ing the child-bearing period treatment should be given; even in latent syphilis where no symptoms are manifest, treatment should be given, as according to our present knowledge a persistently positive Wassermann reaction indicates the presence of living spirochetes in the tissues.

In view of the presence of latent syphilis as revealed by the Wassermann reaction in gynecological patients and the scant attention paid to syphilis as an etiological factor in the production of pelvic pathology in women, a routine Wassermann reaction and the subsequent histo-pathologic study of tissues removed from syphilitics may bring more light to bear upon this neglected phase of gynecology.

A TEST FOR SYPHILIS.—George B. Ubel, Ithaca, New York. *New York Medical Journal*, 1916, vol. civ, 503.

The principles of this test are based upon a few of the recognized facts in chemistry relating to the action of colloids; viz., first, that bacteria react in accordance with all the established facts pertaining to colloids; secondly, one colloid may be absorbed by another colloid preventing its precipitation when a mild precipitant is added. The technic is one previously described by Gordon of Philadelphia, who made no attempt to explain the principle of the reaction. To several c.c. of clear serum in a clean test tube 5 to 10 drops of a 1 to 100 mercury bichloride solution are added. If the serum is nonsyphilitic, a white flocculent precipitate will be formed, giving the serum a turbid appearance in from a few seconds to three minutes and if allowed to stand several hours, the precipitate will settle to the bottom of the test tube. On the other hand if the serum is syphilitic it will remain clear. The technic for testing the spinal fluid is the same as for testing the blood serum, but the results are the reverse; i. e., a nonsyphilitic spinal fluid remains clear and the syphilitic spinal fluid becomes turbulent when the solution is added. The blood should be withdrawn four or five hours after a meal as this insures a serum free from chyle and therefore, much clearer. A clear spinal fluid is also imperative, hence the test should not be attempted on a blood tinged fluid.

THE QUANTITATIVE EFFECT OF SALVARSAN ON THE WASSERMANN REACTION ON THE BLOOD.—John F. King, Jr., Baltimore. *Journal of the American Medical Association*, 1916, vol. lxvii, p. 1669.

In most cases little change occurs in the strength of the Wassermann reaction during the first five days following the administration of salvarsan.

In this series of 20 treatments only one case in the primary stage showed marked weakness of the test. Some previous untreated cases may be given prolonged salvarsan therapy with very little weakness of the Wassermann reaction. Such cases may, however, show strong improvement symptomatically. In this series only one insignificant temporary increase (provocative reaction) in the complement bind-

ing substance could be demonstrated following the administration of salvarsan. It is improbable that over so short a period of time there occurred marked spontaneous fluctuation in the amount of complement-fixing substance in the blood of the syphilitic.

Definite proof of the existence of the provocative Wassermann reaction following salvarsan is not at hand at the present time.

THE SPECIFICITY OF THE WASSERMANN REACTION.—Rudolph Buhman, St. Louis. *Surgery, Gynecology and Obstetrics*, 1916, vol. xxiii, p. 284.

Theoretically the Wassermann reaction is not specific, practically it is highly specific. A strong positive reaction with proper controls and accurately titrated reagents is conclusive evidence of syphilis. The diagnosis of syphilis cannot be made upon a weakly positive reaction without some clinical evidence of the disease and a negative reaction does not exclude a syphilitic infection. Malignant disease does not give a positive reaction.

A COMPARATIVE STUDY OF THE LUETIN AND WASSERMANN REACTION IN INFANCY AND CHILDHOOD.—L. R. DeBuys, and J. A. Lanford, New Orleans. *American Journal of the Diseases of Children*, 1916, vol. xii, p. 587.

The Wassermann reaction is not so valuable as the luetin test in cases of hereditary syphilis.

The authors' series show that it is impossible for a mother to give birth to a child who gave positive laboratory tests for congenital syphilis without herself giving positive tests.

The Wassermann gives evidence of the presence of antibodies in the circulation, indicating an active process; while the luetin not only gives this evidence but also indicates an existing syphilitic condition even though it be inactive. The luetin test is not without its disadvantages, as it requires considerable experience in differentiating the lesion from a simple reaction produced by the intradermal injection of sterile inert foreign material. It is also influenced by the administration of certain drugs. It may give rise to a pseudo-reaction, thereby adding to the possible inaccuracy in the interpretation of its reading.

THE "DELAYED NEGATIVE" WASSERMANN REACTION.—G. M. Olson, Minneapolis. *Journal of Laboratory and Clinical Medicine*, 1916, vol. i, p. 704.

The time in which hemolysis occurs varies very markedly when testing different sera, and if only one reading is taken at the end of two hours, most valuable information will have been lost. Readings should be taken at intervals of 20 minutes and if this is done the "delayed negative" Wassermann will often be found. This "delayed Wassermann" has been found of much greater value than the

slightly positive Wassermann where the test shows only some non-hemolysis at the end of two hours in the incubator.

As guide in the treatment of syphilis, the "delayed negative" is an indication for more treatment, even though the Wassermann is completely negative at the end of two hours in the incubator.

**THE WASSERMANN REACTION IN TWO HUNDRED AND FIFTY-ONE TUBERCULOUS DISPENSARY CASES.**—W. Ray Jones, Seattle, Washington. *Medical Record*, 1916, vol. xe, p. 418.

These were unselected cases coming to the Public Tuberculosis Clinic of the City of Seattle with the ready made diagnosis of tuberculosis. Seventy-three gave a positive reaction and one hundred and seventy-eight a negative.

**THE EFFECT OF POTASSIUM IODIDE ON THE LUTIN REACTION.**—J. A. Kolmer, T. Matsunami, and S. Broadwell, Jr., Philadelphia. *Journal of the American Medical Association*, 1916, vol. lxxvii, p. 718.

Well marked positive luetin reactions were observed among a group of healthy nonsyphilitic persons following the administration of potassium iodide. Similar results were observed among nonsyphilitic persons suffering with various other diseases. Somewhat severe reactions were observed following the intracutaneous injections of 0.1 c.c. of 0.5 per cent agar-agar. The strongest reactions were observed when the luetin was injected during or immediately after the ingestion of potassium iodide. Positive luetin reactions were observed among normal nonsyphilitic persons as late as one month after the ingestion of large doses of potassium iodide. In some instances the administration of potassium iodide caused the site of a former luetin injection to develop inflammatory phenomena progressive to pustulation. Similar but less marked reactions to luetin and agar were observed among guinea pigs and rabbits following the oral administration of potassium iodide.

Accordingly a positive luetin skin test has little value in the diagnosis of syphilis among persons who are taking or who have recently taken potassium iodide. The amount of the iodide capable of producing these reactions varies considerably, also the length of time following the ingestion of iodides when this reaction to luetin may show. For these reasons physicians should very carefully rule out the possible influence of iodides before conducting the luetin skin test.

**THE VALUE OF THE WASSERMANN TEST IN PREGNANCY.**—G. H. Fall and G. G. Moore, Chicago. *Journal of the American Medical Association*, 1916, vol. lxxvii, p. 574.

The serums studied were obtained in a routine examination of the cases in the obstetric ward of the Cook County Hospital of Chicago and from a few private hospitals. The majority were from the ninth

month to term. The following conclusions are drawn: The Wassermann reaction is of great value in diagnosis in pregnant women in whom the condition is usually latent. The diagnosis of this condition in mothers with the institution of proper treatment will prevent the increase of syphilitic children, and those born can be properly treated as early as possible. The majority of mothers having syphilis are ignorant of their condition and therefore improperly treated.

In a series of 160 pregnant women, 11.3 per cent positive Wassermanns were found. In 116 married women 10.6 per cent gave a positive reaction; in 44 single women 13.5 per cent gave a positive reaction. White women were positive in 9.5 per cent of cases, colored women in 28.5 per cent. Only one of 18 giving a positive reaction had a history of syphilis, 6 gave histories of previous abortions and three had syphilitic complications of pregnancy as eclampsia, and mental psychoses.

**THE INFLUENCE OF POTASSIUM IODIDE ON THE LUTIN TEST.**—Randolph Lyons, New Orleans. *Southern Medical Journal*, 1916, vol. lxvii, p. 487.

The experiments performed fully confirm the observation of Sherrick upon the influence of potassium iodide on the luetin reaction. That iodine is the essential factor in producing a positive reaction in a nonluetin individual is demonstrated by the fact that hydriodic acid, thyroid extract and hyperthyroidism will produce a similar effect.

When a luetin test is made it is essential that no iodine in any form be taken internally, furthermore it is important that no iodine should have been ingested for an interval of at least three weeks previous to the performance of the test.

Torpid or late reactions occurring after an interval of two weeks are usually due to the ingestion of potassium iodide. The reaction may be influenced after an interval of two months by the subsequent administration of potassium iodide. Anomalous reactions may generally be attributed to potassium iodide.

Activation of the luetin test with mixed treatment vitiates it. Clinical differentiation between the luetin reaction, and the iodide reaction cannot be made with any degree of certainty. When a positive test develops very rapidly, an iodine reaction may be suspected. The extreme prevalence of the use of iodine in some form will necessitate a critical review of the published reports of positive reactions in order to eliminate the iodide reaction. This will undoubtedly lower the percentage of positive results.

**SYPHILIS OF THE NERVOUS SYSTEM.**—Eugene D. Bondurant, Mobile. *New York Medical Journal*, 1916, vol. civ, p. 97.

Ptoxis and other oculomotor palsies are usually diagnostic of meningeal syphilis of the base. Most atrophy of the optic nerve is syph-

ilitic in etiology. Chronic neuritis of sensory type is usually syphilitic. Symptoms of spinal sensory root irritation, stabbing pain, anesthesia, disorder of position sense, delay in rate of transmission of nervous impulses, etc., are usually symptoms of syphilitic disease.

The onset of epilepsy after the age of 35 years means a syphilitic infection. The occurrence of arteriosclerosis, cerebral hemorrhage, softening, etc., before the age of 35 years is seen only in those previously infected by syphilis. Nearly all spastic paralysis is syphilitic in origin and nearly all disturbances in gait are due to syphilis. Most aphasia and other speech defects in adults are due to syphilis. A large percentage of cases of acute and chronic mental diseases are primarily syphilitic in causation.

**SYPHILIS WITH NEUROLOGIC SYMPTOMS SIMULATING OTHER CONDITIONS.**—D. A. Haller and I. C. Walker, Boston. *Journal of the American Medical Association*, 1916, vol. lxxvii, p. 1497.

The etiologic relationship to syphilis of the cases reported would pass unnoticed but for the positive Wassermann reaction. With the recognition of the incidence of syphilis and of the probability that syphilis may be the cause of the symptoms in a given case, the inauguration of antisymphilitic treatment is often followed by excellent results. The cases reported resembled conditions among which may be mentioned, amyotrophic lateral sclerosis, spastic paraplegia, multiple sclerosis, and pseudotumor cerebri and cerebelli. In the cases detailed, syphilis is considered to be the cause in each case, both because of the positive Wassermann reaction, and because of the improvement following antisymphilitic treatment.

**CLINICAL COURSE AND PHYSICAL SIGNS IN HEREDITARY SYPHILIS OF EARLY AGE.**—Abner Post, Boston. *American Journal of Diseases of Children*, 1916, vol. xii, p. 364.

One of the early symptoms which ought to attract attention is obstinate wakefulness. Nasal catarrh attacks a very large portion of syphilitic infants and gives rise to a most characteristic symptom. Few children with the "snuffles" of hereditary syphilis escape a diagnosis of adenoids and an operation. Syphilitic babies, especially those in whom the "snuffles" is marked, have also a peculiar cry which is at once hoarse and high pitched. The marasmus of syphilis sometimes appears in infants who show in themselves little other evidence of the disease and continues until the baby is reduced to the condition of a living skeleton. The syphilitic infant gains weight very slowly even in spite of the utmost care in feeding. The peribronchial glands occasionally play an important part in the clinical history of the affected child. The skin lesions of hereditary syphilis are marked by a tendency to become confluent and form large plaques, and also to desquamate and ulcerate, the most common eruption being the maculopapular. Onychia of the nails is quite



common in syphilitic infants. Loss of hair is one of the most important characteristics.

Cranial exostoses have four seats of predilection, the two frontals and the two parietals. Two pairs of twins are mentioned. Of the first pair, one has well marked snuffles, marked pallor, maculapapular eruption and other evidences of syphilis. The second baby had a much better appearance, but had a confluent macular eruption. In the second pair of twins the children are about equally affected and both are markedly syphilitic.

The diagnosis of hereditary syphilis in the infant may be the simplest possible in the severe cases in which the wasting and external manifestations are prominent, or it may present one of the most difficult problems in medicine.

FETAL AND PLACENTAL SYPHILIS.—E. D. Plass, Baltimore. *American Journal of Obstetrics and Diseases of Women and Children*, 1916, vol. lxxiv, p. 561.

During the past four years autopsies were done on seventy-five babies dead from all causes, and the organs studied for the presence of the spirochete; and the placenta, for the histological evidences of syphilis. The syphilitic placenta was noted in twenty-seven cases and in six other cases it was suspicious, whereas spirochetes were demonstrated thirty-four times.

Among forty-two macerated fetuses there were twenty-three which were definitely syphilitic, a percentage of 54.8. This differs considerably from the usual statement that 80 per cent of macerated fetuses are luetic.

The Wassermann reaction was performed on the mother's blood in forty-seven cases and the results show rather wide discrepancies when compared with the other findings. Thus in twenty-three cases where the placenta was normal and the spirochete could not be demonstrated, the Wassermann was positive in eight cases.

The Wassermann on the fetal blood was done only in ten cases, but it is interesting that it always gave a result that was confirmed by the presence or absence of the spirochete. The following conclusions are drawn:

1. The syphilitic placenta is characterized by increased size and weight, abnormal proliferation of the stroma cells and an obliterative endarteritis and endophlebitis. For practical purposes the changes are specific and form very strong evidence of the presence of fetal syphilis, whereas their absence does not exclude the disease.

2. The demonstration of the *Treponema pallidum* in the fetal tissues affords an absolute diagnosis of lues, but the failure of demonstration proves nothing.

3. There are many discrepancies between the histopathological findings in the placenta and fetal tissues and the maternal Wasser-

mann reaction and it is believed that the complement fixation test on the mother is of less value in correctly diagnosing fetal syphilis than the other two methods.

4. The diagnosis of fetal syphilis should be attacked from all points and absolute reliance should not be placed upon any one method of diagnosis.

HEREDOSYPHILITIC DENTAL STIGMATA.—John B. Stein, New York. *Medical Record*, 1916, vol. xc, p. 445.

The diagnostic significance of syphilitic dental stigmata is of great importance:

1. In detecting heredosyphilis; because the stigmata are at times the only evidences of this disease.

2. In tracing, in a patient with these stigmata, the possible syphilitic origin of some condition the cause of which was unknown and was not suspected of being syphilitic.

3. In tracing back the existence of syphilis, as, for example, in diagnosing the condition of a woman (the mother of a child when she has no manifestations and gives no history of the disease), and examination of her children's teeth may prove her to have had syphilis; and so in diagnosing a younger child's condition (an epileptic for example) the examination of an older brother's or sister's teeth may alone reveal or lead to a discovery of the diseased syphilitic condition through which the younger had passed.

4. In life insurance examinations.

5. In the effective administration of the efforts of all interested in dental, oral, social, moral, and mental hygiene.

### Prophylaxis

SYPHILIS IN ITS RELATION TO PUBLIC HEALTH.—Lloyd Thompson, Hot Springs, Arkansas. *Southern Medical Journal*, 1916, vol. ix, p. 879.

It is possible with certain units of population such as those in hospitals, prisons, etc., to make surveys in regard to syphilis. Such a survey was performed by the writer in the Arkansas State Hospital for Nervous Diseases where 33 per cent of 1000 tests were found to give positive results.

It devolves on society to institute measures for the prevention of venereal disease. Such methods consist of education and personal and public prophylaxis.

The control and medical examination of prostitutes does not reach clandestine prostitution which is a great source of syphilitic infections. The segregation of syphilitics is impossible in our present stage of social development. The final solution of the problem con-

sists in the registration of all cases and the institution of vigorous treatment.

A marriage license should not be granted without a thorough physical examination and a negative Wassermann reaction showing the probable absence of syphilis.

THE MEDICAL PROFESSION AND THE CAMPAIGN AGAINST VENEREAL DISEASE.—Otto May. *Lancet*, 1916, vol. cxi, p. 893.

May, as Secretary of the *National Council for Combating Venereal Diseases*, states that the two chief objects to be attained are: (1) education of the general public in the significance of the diseases, their racial and economic effects, the importance of thorough and early treatment, and the dangers of neglect; (2) the provision of wide facilities for the free diagnosis and treatment of the diseases by modern methods. The Commission recommends that the obligation should be impressed upon all doctors who treat syphilis and gonorrhea in institutions or privately to hand cards of instruction and warning to their patients.

#### CARD FOR SYPHILIS.

1. Syphilis is a contagious disease; it can be cured if promptly treated by a doctor.
2. Treatment by quacks, herbalists or persons advertising so-called nature cures is likely to lead to disastrous results.
3. The infection may last several years. It can be conveyed to others by sexual intercourse, by kissing, or by using the same eating or drinking utensils or tobacco pipes, etc.
4. Treatment should not be stopped until the doctor says this may be safely done.
5. Should signs or symptoms of the disease appear, such as rashes on the skin, sore throat, or symptoms of nervous disease, a doctor should at once be consulted.
6. A doctor should be consulted occasionally, even though there are no symptoms of a return of the disease.
7. Treatment need not, as a rule, interfere with work or necessitate stay in hospital.
8. No one who has, or has had, syphilis should marry without permission of the doctor; otherwise there is great danger of giving the disease to wife or children.
9. Teeth should be cleaned night and morning. The patient should dress warmly, live simply, and avoid wine, beer, spirits, and other intoxicants.

#### Treatment

THE TREATMENT OF SYPHILIS OF THE TESTICLE WITH SALVARSAN AND NEOSALVARSAN.—George Barraud, Paris. *American Journal of Urology and Sexology*, 1916, vol. xii, p. 450.

Syphilis of the testicle properly speaking presents itself in three pathologic forms; namely, sclerogummatous form, which is by far the most frequent; the uncommon gummatous; and the sclerous form

which is often the outcome of two preceding types. In the immense majority of cases of testicular syphilis, mixed treatment gives excellent results but it happens occasionally that it is powerless or is badly tolerated. Salvarsan and neosalvarsan given in prudent but sufficient doses and excepting in cases presenting a contraindication acts very rapidly, very efficaciously in the sclerogummatous and gummatous types of syphilis of the testicle, even when fistulæ have formed. The drugs can even cure cases where a well directed and prolonged mixed treatment has failed. Neosalvarsan is a means of treatment of the highest practical value and in certain cases is the most efficacious treatment of syphilis of the testicle.

THE PRINCIPLES OF THE TREATMENT OF SYPHILIS.—S. Pollitzer, New York. *Journal of Cutaneous Diseases*, 1916, vol. xxxiv, p. 633.

Specific therapy should be instituted at the earliest possible moment after a positive diagnosis is made. Three injections of salvarsan should be administered in large doses at intervals of twenty-four hours and followed by a course of eight weekly injections of salicylate of mercury. If the treatment was begun before the appearance of roseola, there is a strong presumption of a cure, and the case may remain under observation without further treatment. When the treatment is begun after the appearance of a rash, the first course of salvarsan and mercury is repeated, after a pause of two months, and again after another similar interval. After three courses within the first year, if the Wassermann reaction has remained negative, further treatment may await the reappearance of a positive Wassermann reaction.

In cases which come under treatment a year or more after infection, treatment should be continued until the Wassermann reaction becomes negative and thereafter two more courses of treatment should be administered even though the Wassermann reaction remains negative. If a year or more of constantly negative Wassermann reaction without treatment the cure should be tested by a provocative injection of salvarsan and by an examination of the spinal fluid. The writer employs the provocative salvarsan test in deference to current opinion, however, he is not entirely convinced of its value and is now engaged in a study of the question.

SALVARSAN IN THE TREATMENT OF DOUBLE INFECTION, TUBERCULOSIS AND SYPHILIS.—Nathaniel Bowditch Potter, New York. *American Journal of the Medical Sciences*, 1916, vol. cliv, p. 823.

The prompt employment of salvarsan or neosalvarsan is indicated in latent, chronic and moderately active tuberculosis: (a) as soon as the nature of an added infection is diagnosed with reasonable probability to be syphilis; (b) whenever the history, signs or symptoms strongly suggest the presence of luetic infection particularly if such

a patient is not improving upon the usually successful, hygienic and climatic treatment for tuberculosis; but (c) active tuberculosis, acute tuberculosis, and diffuse miliary tuberculosis are usually definite contraindications to the use of these new arsenic preparations although in both the first two mentioned groups there will be found manyluetie patients upon whom smaller doses of salvarsan may well be tried and, unless followed by untoward effects, cautiously repeated in gradually increasing doses. When tubercular infection once becomes active in a patient with secondary, tertiary or even latent syphilis a careful employment of one of these drugs is also indicated. The more active the tuberculosis, the smaller should be the initial dose, the slower its increase, the less frequent the interval, and the greater care and watchfulness required. Tuberculin-like focal reactions may follow their administration, should be carefully watched for and if present, the location, intensity and character will frequently guide in the selection of the appropriate dose or interval.

**DEATH FOLLOWING INTRAVENOUS INJECTION OF SALVARSAN; TWO CASES.**—W. Kerl, *Wiener klinische Wochenschrift*, 1916, vol. xxix, p. 1227.

The autopsy findings in two cases seem to indicate that a lowered vitality particularly on the part of the lymphatic and vascular systems is the most common cause of accidents with salvarsan. Before undertaking salvarsan treatment, the condition of the vessels, especially of the brain, should be investigated with particular care.

**THE RESULTS OF TREATMENT IN ARTERIAL HYPERTENSION DUE TO OR ASSOCIATED WITH SYPHILIS.**—Louis A. Levison, Toledo, Ohio. *Journal of the American Medical Association*, 1916, vol. lxvii, p. 730.

Antisypilitic treatment is not to be expected to reduce high blood pressure in syphilitics who have unusual arterial hypertension, occasional reductions in the blood pressure in such cases do, however, take place. The association of arterial hypertension with syphilis does not contraindicate the treatment of the latter. The careful use of mercury and salvarsan has not had bad results on the kidneys damaged by arterial disease.

**THE INTENSIVE TREATMENT OF SYPHILIS.**—Lloyd Thompson, Hot Springs, Arkansas. *Journal of the American Medical Association*, 1916, vol. lxvii, p. 734.

The logical method of treating syphilis is to administer mercury and salvarsan as intensively as the patient can tolerate in all cases, and iodine in some form where indicated. The treatment should be

started as quickly as possible after a diagnosis of syphilis has been made. It is not necessary to subject the patient to a short course of mercurial treatment before beginning salvarsan.

For intramuscular injection mercuric benzoate is preferable. All cases of syphilis of the central nervous system should have intraspinal medication. A combination of the Ogilvie and the Wile methods is used. Novocain intraspinally eliminates, to a great extent, the pain in the back and legs which so frequently follows these injections.

The patient should not be discharged as cured until the following conditions have been fulfilled: (1) a clinical cure; (2) a constantly negative Wassermann on the blood at frequent intervals for a period of two years following the last treatment; (3) a negative spinal fluid at periods of one or two years following the last treatment.

HOW SHALL LATENT SYPHILIS BE TREATED?—H. C. Solomon, Boston.  
*Interstate Medical Journal*, August, 1916.

In the course of syphilis, the latent period represents merely a shorter or longer remission. A positive Wassermann reaction, indicative of latent syphilis, is an indication for careful examination, lumbar puncture and antisyphilitic treatment. The primary and secondary symptoms of syphilis, in comparison with the later manifestations, are relatively benign. Adequate treatment during the period of latency is insurance against dangerous or incurable conditions of the later stage. It is essential for the prevention of physical and mental disease. Treatment should be continued until the patient can be declared cured.

SOME GENERAL INFORMATION CONCERNING THE DIAGNOSIS AND TREATMENT OF SYPHILIS.—Captain M. A. Reasoner, Medical Corps, United States Army. *The Military Surgeon*, 1916, vol. xxxix, p. 253.

In the presence of suspicious manifestations, one or more negative Wassermann reactions is not sufficient evidence upon which to base a diagnosis.

The greatest good will be accomplished by the administration of both salvarsan and mercury. The best results are to be expected when treatment is begun early. Mercury should be pushed to the physiological limit. The soluble salts of mercury have some points of superiority over the insoluble salts. The results obtained from inunction, when properly given, compare favorably with those from any other form of mercurial administration.

It is believed that syphilis is curable in a certain per cent of cases. The results obtained from spinal fluid examinations are of great

value. Information may be obtained from the provocative Wassermann reaction which can be secured in no other manner.

The luetin reaction has its greatest value in the diagnosis of hereditary and tertiary syphilis, tabes, paresis and old cases of cerebrospinal syphilis.

**SYPHILIS OF THE NERVOUS SYSTEM.**—B. R. Tucker and H. J. Hayes, Richmond. *Southern Medical Journal*, 1916, vol. ix, p. 765.

The authors have been able to obtain a decided clinical and serological improvement in a number of cases, which fall into the groups of cerebral, cerebrospinal and spinal syphilis using salvarsan intravenously in conjunction with mercury and iodides. The introduction of old salvarsan into the cord is attended with little or no real danger provided ordinary care is exercised. Neosalvarsan should never be used as it is not a stable compound. Salvarsan intravenously is very efficient in those cases of superficial involvement of the nervous system manifested by headache, slight grades of cranial palsy andluetie vascular conditions. Mercury and iodide should be included in the medication in syphilis of the central nervous system. Mercury by inunctions has given the best results. Several weeks of almost absolute rest frequently produce a marked improvement.

**TREATMENT OF SYPHILIS OF THE CENTRAL NERVOUS SYSTEM.**—Homer F. Swift, New York. *American Journal of the Medical Sciences*, October, 1916.

In the intraspinal treatment of syphilis of the central nervous system the preparations, which have stood the test of time, are: (1) the serum obtained from patients shortly after intravenous injection of salvarsan; (2) serum to which small quantities of salvarsan have been added; (3) neosalvarsan in small quantities and weak concentration; (4) mercurialized serum.

As to the direct application of mercury in the form of an albuminate, the reports seem to indicate that if the amount of mercury is kept under the irritating dose, beneficial results may be expected from its injection.

The injection of neosalvarsan in concentrated solutions or even in one to one thousand solutions has been proved to be a dangerous procedure. The addition of small quantities of salvarsan to serum is followed by a distinctly beneficial result provided that the dose never exceeds .5 mg. Some cases receiving only normal serum seem to have been benefited.

The technic now employed consists of bleeding the patient one-half hour after intravenous treatment and injecting 15 c.c. of whole heated serum. Most of the patients now receive both the intravenous and intraspinal injections on the same day and return to their usual occupation the following day. The treatments are better borne if not repeated oftener than once in two weeks.

One general principle which should always be considered is that in any patient who shows evidence of involvement of the cerebral meninges or brain, salvarsan treatment should be preceded by a short course of mercury to prevent the possible occurrence of a Herxheimer reaction in the region of the vital nervous centers. In the meningitis of the secondary period the response to alternate courses of salvarsan and mercury has been prompt and permanent.

In the tertiary forms of the disease, the so-called interstitial forms, alternate courses of mercury and iodides and of salvarsan are usually followed by decided improvement.

In tabes, because of the apparent sensitiveness of many cases to mercury, it is better to start the treatment with small intravenous doses of salvarsan, gradually increasing and giving a treatment every week for a course of six to eight injections.

Compared with the results of other forms of lues of the central nervous system, the treatment of paresis has been disappointing.

In the treatment of syphilis of the central nervous system the objects of therapy are three fold: (1) the cure of the disease; (2) the amelioration of the symptoms; (3) the prolongation of life. With the possible exception of paresis, all these objects may be attained in most cases of syphilis of the central nervous system. To be satisfied with the attainment of the last two without attempting to attain the first is to fail to apply all of the means at our disposal.

THE TREATMENT OF SYPHILIS OF THE NERVOUS SYSTEM.—First Lieutenant A. S. Clark, M.R.C., United States Army. *The Military Surgeon*, 1916, vol. xxxix, p. 616.

After having observed the results of a large number of cases treated after the various methods in different clinics, Clark has adopted a modification of the Ogilvie method as used in Fordyce's Clinic at Columbia: 50 c.c. of blood are withdrawn from the patient, or from another syphilitic patient and immediately centrifuged at 3000 revolutions for 17 minutes. One decigram of salvarsan is dissolved in 30 c.c. of freshly distilled, boiled water and very carefully neutralized with a four per cent solution of sterile filtered sodium hydrate. Ten c.c. of this solution are then diluted up to 33 c.c. with boiled distilled water so that each cubic centimeter contains one milligram of salvarsan. To five to ten c.c. of the centrifuged blood serum is added whatever fraction of a cubic centimeter of the prepared salvarsan solution will give the desired fraction of a milligram of salvarsan,  $1/10$ ,  $1/5$ ,  $1/4$ ,  $1/2$ , and this mixture is incubated at  $37^{\circ}$  for 45 minutes and inactivated at  $57^{\circ}$  C. for 30 minutes. The solution is then ready for administration and in no case has over  $1/2$  of a milligram been given and then only after a series of gradually increased smaller doses. Symptomatically a marked improvement often occurs in cerebrospinal syphilis when there is no destruction of the parenchyma.



The pain of tabes, ataxia, bladder and other disturbances are often relieved at least temporarily, but the knee jerks and pupillary reactions are difficult to change apparently.

CEREBRAL SYPHILIS.—M. J. Karpas, New York. *Interstate Medical Journal*, August, 1916.

In syphilis of the nervous system the examination of the cerebrospinal fluid is of vital interest and indeed infrequently without such an aid a diagnosis is not possible. There are five important reactions, (1) lymphocytic phenomenon, (2) the globulin content, (3) the gold-sol test, (4) the Wassermann test of the fluid, (5) the Wassermann test of the blood. For practical purposes and particularly for therapeutic indications it is deemed advisable to divide cerebral syphilis in the following groups: (1) meningitic, (2) gummatous, (3) endarteritic, (4) mixed, (5) degenerative.

In the acute meningitic form of cerebral syphilis, the prognosis is relatively good, and under active and persistent treatment, recurrence may be obviated.

The outlook in chronic meningitis is not very encouraging because the patient does not yield readily to therapeutic measures, and furthermore defect symptoms frequently remain.

In cerebral gummata partial or complete restoration is possible depending, however, upon the intensity of the injury sustained by the nervous tissues.

In the endarteritic form the outlook is decidedly poor.

In all cases where the usual contraindications are wanting, salvarsan and neosalvarsan should be administered. It is always wiser to begin with a small dose in order to test the patient's constitutional tolerance. On the day following the administration of salvarsan, mercury injections or inunctions with potassium iodide should be given. Mercury salicylate is preferred, never exceeding one-half grain at the first dose gradually increasing until constitutional tolerance has been attained.

Intraspinal treatments of salvarsanized serum and mercury serum are decidedly efficacious in the treatment of cerebral syphilis.

SYPHILIS OF THE NERVOUS SYSTEM.—John A. Fordyce, New York. *Medical Record*, 1916, vol. xc, p. 575.

In a series of cases of secondary syphilis examined in the author's hospital service two years ago less than 20 per cent revealed abnormalities in the spinal fluid. Recently another series of 63 cases were punctured; 10 showed very slight changes as to lymphocytosis and globulin content, coming well within the border line case, while 15 exhibited a definite increase in cells and globulin with positive Wassermann in seven. Thus 25 per cent of the cases gave evidence of a

definite pathological condition of the cerebrospinal axis, while 16 per cent showed trifling abnormalities.

Our greatest hope in the cure of syphilis of the nervous system lies in the adequate handling of the infection in its early inception, in other words it must be prophylactic. The treatment should consist of a combination of salvarsan and mercury, for we have learned that salvarsan alone is apt to be followed by neuro-recurrences. Since the introduction of the intraspinal method in 1912 by Swift and Ellis, the author has treated in his private work and in the Vanderbilt Clinic 110 cases of tabes, 13 of taboparesis, 12 of optic atrophy, 25 of paresis, and 20 cases of other types of cerebrospinal syphilis.

At first the original method of Swift and Ellis; namely, the use of autosalvarsanized serum was adhered to; for the past two years the modification of Ogilvie with the direct addition of salvarsan to the blood serum.

In active progressive tabes the lancinating pains are ameliorated or disappear entirely. The gastric and rectal crises are usually controlled or regress and the ataxia is markedly decreased and in some cases has disappeared. Disturbances of sensation partially or completely clear up. Sphincter control and sexual power have improved or returned to normal. The patients feel better, put on weight, and are able to resume their occupations. No return of absent reflexes has been noted.

In the type of paresis with the preponderant changes in the menovascular structures with a high cell count, a rather sudden onset and marked mental disturbance, good results can be obtained and the process perhaps kept stationary. Where the parenchymatous tissue is severely involved with atrophy or sclerosis attended by a low lymphocytosis, and an insidious onset, the degenerative changes have probably advanced too far, and at most, only temporary improvement can be expected with almost certain relapse.

All patients at the end of the first year of their infection should be punctured whether or not they have manifestations or positive signs of the disease.

THE INTRASPINAL TREATMENT OF SYPHILIS OF THE CENTRAL NERVOUS SYSTEM.—A. Roëke Robertson, Captain C. A. M. C. The British Medical Journal, October 7, 1916.

The author reports eight cases which were treated by the Swift-Ellis method. The consideration of these cases from both a clinical and laboratory standpoint shows us that we have a powerful form of therapy in the combined intravenous and intraspinal treatment. Whether the improvement will be lasting in these cases time alone will tell. Though the results resemble very closely those of other workers using the same method and claiming good results, the author

feels that this system of treatment is destined to undergo changes ere we arrive at an ideal method.

TREATMENT OF HEREDITARY SYPHILIS.—Philip H. Sylvester, Boston.  
American Journal of Diseases of Children, October, 1916.

A hypothetical patient would receive the following treatment:

1. During pregnancy the mother would be vigorously treated.
2. At birth irrespective of lesions or the Wassermann reaction he would receive inunctions of twenty-five per cent mercurial ointment for about two weeks during which time if lesions appear or if the patient got worse he would immediately receive .15 or .2 gm. neosalvarsan in 5 c.c. of distilled water intravenously at weekly intervals, meanwhile continuing the mercury.

Tardy or late types are divided in two groups. The first present lesions in bones, joints, eyes and teeth, develop gummata and produce general malnutrition. The second group represents lesions of the central nervous system.

In the Children's Hospital in Boston, over one hundred patients with hereditary syphilis have been treated in the last two years, fifty-eight of whom have developed enough clinical evidence to be of value. Of the early types there were fifty patients mostly under six months old; eighteen of whom received mercury alone, thirteen by inunction, and five mercury with chalk. None died and all did fairly well, were clinically free from signs, and for two to six months all those treated over six months were apparently as healthy as the average baby. Seventeen patients, who were very sick and who would probably have died within a few days on mercury alone, were treated with neosalvarsan; of the seventeen only four died, one in two days, one five days, and two between two or three weeks after treatment. The remaining thirteen of the seventeen desperately sick babies are now after a period of months as well as the average baby. Nine other patients not desperately sick were treated by neosalvarsan and mercury. In them the effect of the neosalvarsan was even more rapid than in the desperately sick child and caused the disappearance of mucocutaneous lesions.

The maximum dose of neosalvarsan has been .4 gm. in babies of one and a half years or over. One month or under the dose is .1 gm., from one to six months .2 gm., from six months to a year .25 gm. and from one to one and a half years .25 gm. to .35 gm. The drug is given intravenously in 5 c.c. of freshly distilled water and repeated weekly until all evidence of syphilis except the Wassermann reaction has disappeared.

Some of the conclusions are: fetal syphilis should be treated by treating the pregnant syphilitic mother vigorously.

Arsenic should be used in fairly large doses if immediate intensive

action is desired. Mercury in one form or other should be used in conjunction with arsenic and continued for a long time after evidences of the disease have disappeared.

Treatment should be persisted in for at least two years after which a negative Wassermann after six months without treatment may be considered evidence of a cure.

Neosalvarsan appears to be the most favored arsenical.

Lesions other than of the central nervous system may be readily relieved. To date the therapy of the lesions of the central nervous system is disappointing but not discouraging.

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## Original Articles

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### SPIROCHÆTES\*

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*From the Rockefeller Institute for Medical Research*

(Received for publication, March 1, 1917)

TODAY a spirally shaped microorganism may be called either *Spirochæta*, *Spirillum*, *Treponema*, *Spironema*, *Cristispira*, or *Saprospira*, according to the characteristics of the organism. The choice of the generic name for a given variety is still very much dependent upon the individual view held by different investigators, and this has led to a somewhat chaotic state of affairs in the nomenclature of this group of organisms. This is found to be the case more especially in the medical literature where these minute spiral organisms play an important part as causative agents of certain diseases. Nevertheless, thus far but little attention has been paid to the systematic position occupied by them. Since Ehrenberg,<sup>1</sup> in 1838 introduced a new generic term "*Spirochæta*" to designate a free living spiral organism which he found in a swamp near Berlin, it remained practically unnoticed until 1904 when Schaudinn<sup>2</sup> stated as his view that so-called *Spirochæta* constitutes a phase of the life cycle of trypanosomes; hence, that they are of protozoan origin instead of being plants. It may here be mentioned that Ehrenberg, Migula, and other systematists classified the *Spirochete* under *Bacteria*, which classification was accepted for nearly seventy years. Indeed, it was not uncommon among medical authorities to employ the terms *Spirochæta* and

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\*Harvey lecture delivered on February 5, 1916, at the New York Academy of Medicine.

*Spirillum* interchangeably. Medical men may consider the causative agent of relapsing fever as being a *Spirillum* or a *Spirochæta*, according to their inclination. This sort of indiscriminate use of terms has gradually extended to other spiral organisms, such as the causative agent of syphilis. According to the old school it was of very little importance whether a spiral organism had one or two polar flagella or a tuft of flagella, so long as both *Spirochæta* and *Spirillum* belonged to the same family. On the other hand, Schaudinn and his school maintained that the difference between *Spirochæta* and *Spirillum* is no longer so easily disposed of since one is of plant and the other of animal origin. The revolutionary view of Schaudinn was based chiefly upon his observations on a protozoon. *Leucocytozoon ziemanni* is regarded by Schaudinn as a trypanosome found in the blood of the little owl (*Athene noctua*), which is said to undergo a spirochætal stage while passing through an intermediary host. While the accuracy of Schaudinn's observations has been questioned by later investigators,<sup>3, 4, 5</sup> the great impetus which his theory occasioned has had a far-reaching effect upon the development of our present knowledge concerning the organisms generally known as "spirochætes." It was soon after announcing his views that Schaudinn made his famous discovery of the occurrence of *Spirochata pallida* in syphilis. In their first publication Schaudinn and Hoffmann<sup>6</sup> gave the name "*Spirochata pallida*" to the spiral organism found in syphilitic lesions because of its resemblance to *Spirochætes* in general, but within a year Schaudinn recognized certain features (preformed cylindrical spiral filament, difficulty in staining, regularity of curves, etc.), which he considered distinctive enough to classify it apart from the usual *Spirochætes* (exchangeable curves, taking on of a violet component of Giemsa, no preformed spiral, ribbon form, etc.).<sup>7, 8</sup> Thereupon he replaced the generic name *Spirochæta* with a new term *Treponema*.<sup>9</sup> This all occurred in 1905. But before Schaudinn had had time to decide upon a new generic name for his organism, Vuillemin<sup>10</sup> (1905) proposed that it be called "*Spironema*." In the meanwhile some authors, particularly in France, commenced to use the term "*Spirille*." There were also some newer generic names created by still later systematists, such as *Microspironema*<sup>11</sup> (Stiles and Pfender\*) *Borrelia*<sup>12</sup> (Swel-

\*The statement of some authors (Gross and Gonder) that this antedated Schaudinn is erroneous. Schaudinn published his note on October 19, and Stiles and Pfender on December 2 of the same year.

lengrebel), Spiroschaudinna<sup>13</sup> (Sambon), and Spirosoma<sup>14</sup> (Schilling), but these are of no importance today. The only difficulty in choosing the generic name for "Spirochæta pallida," lies in the fact that although Schaudinn corrected his error within several months after his discovery, another suggestion had meanwhile been made to answer the same purpose, and according to the international code of nomenclature, Vuillemin's Spironema would have had to receive preference over Schaudinn's own Treponema, had it not been for the fact that the term Spironema as proposed by Vuillemin is not acceptable to those who maintain, like Schaudinn, that the organism of syphilis belongs to the protozoa, because in 1892 it was used by Klebs as a genus of Flagellate.<sup>15</sup> The same name had also been used by Meek in 1864 for a fossil snail. Of course, "Spironema" may be available for any one who holds that "spirochetes" do not belong to Protozoa.\* Thus, Gross<sup>16</sup> (1910) used this term to include various spirochætes allied to the spirochætes of relapsing fevers, syphilis, etc., with the specification that he believed these to be of bacterial nature. It may be mentioned that the term "Spirochæta," as taken up by Schaudinn in 1905 in the sense of protozoan organism, had already been used by Michael Sars in 1856 for an annelid genus. It seems that the creation by Schaudinn of the genus Treponema was perfectly justified, although not all the characteristics attributed by him to this genus are found to be distinctive from those of other "spirochætes." Schaudinn did not live long enough to witness the gradual modification which the Spirochæta question went through. As a result of the works of various systematists and zoologists, we are brought to realize that the original *S. plicatilis* described by Ehrenberg in 1838 is an entirely distinct organism and bears little relation to the other organisms which we now call "spirochætes." We also know that the latter should no longer be designated as spirochætes, and that the spiral organisms found in the crystalline style of various mussels are neither trypanosomes, as held by Perrin,<sup>17</sup> nor typical spirochætes, but from another group which may be seen to possess one or more genera. These facts were revealed after the death of Schaudinn by the careful studies of Novy and Knapp,<sup>18</sup> Schellack,<sup>19</sup> Gross,<sup>20, 21</sup> Zuelzer,<sup>22</sup> Gonder,<sup>23</sup> Dobell,<sup>24, 25, 26</sup> Hoelling,<sup>27, 28</sup> Fan-

\*The use of two identical terms, one in the animal and the other in the plant kingdom, has been known to occur and is permissible. For example, "Bacillus" and "Coccus" are found in zoological as well as in botanical genera.

tham,<sup>29, 30</sup> Swellengrebel,<sup>31</sup> Bosanquet,<sup>32, 33</sup> and others. Although much light has been thrown upon the structure of these organisms, no definite conclusion has yet been reached as to the affinity of the "spirochaetes" in the system of natural history. While there are still some who consider "spirochaetes" as allied to bacteria and others who regard them as of a protozoan nature, there now appear to be certain authors who are inclined to set them apart both from bacteria and protozoa, and classify them apart in the domain of the Protista, i. e., belonging to neither plant nor animal. Dobell<sup>24</sup> represents this view, and Doflein<sup>34</sup> compromises by calling them "Proflagellate," and placing them between Bacteria and Protozoa. Zuelzer<sup>22</sup> holds a somewhat similar opinion to that of Dobell. In order to bring up some of the more important data relative to the question of classification, we shall now review the present situation.

As remarked at the beginning of this paper the Spirochaeta of Ehrenberg was regarded as a genus of the family of Spirillaceae, and no question was raised in regard to its possible affinity with the Protozoa until the publication of Schaudinn's fascinating observations on *Leucocytozoon ziemanni*. Since that time there have appeared numerous partisans of Schaudinn's view that so-called spirochaetes are of protozoan nature. Their main contentions are as follows: (1) Longitudinal division as the mode of multiplication, (2) presence of an undulating membrane; (3) high degree of bodily flexibility; (4) absence of cell membrane; (5) absence of a motor organ such as the flagella; (6) presence of a periplastic process; (7) peculiar nuclear arrangement; (8) band-like bodies; (9) encystation or resistant form; (10) a certain periodicity in their pathogenic activity in the infected hosts, and (11) effect of certain chemicals such as sodium taurocholate, saponin, etc., which bring about the dissolution of these spiral organisms and thus offer a contrast to the great resistance shown by bacteria (especially spirillum) to these substances. The foregoing characteristics tended to place the Spirochaete in the Flagellate group, but subsequent studies by different investigators, especially those who have employed a more recent and approved cytological technic seem to indicate that many of the above criteria were based upon erroneous or insufficient observations. According to the observations of Dobell,<sup>24</sup> Gross,<sup>16, 20, 21</sup> Zuel-



zer,<sup>22</sup> Swellengrebel,<sup>31</sup> Novy and Knapp,<sup>18</sup> and others, the following features are characteristic of "spirochetes."

1. In the case of the majority of "Spirochetes" transverse division is the only mode of multiplication (Koch, Levaditi, Fraenkel, Novy and Knapp, Borrel, Gross, Zuelzer, Swellengrebel, Schellack, etc.). Only in certain pathogenic small varieties has the occurrence of longitudinal division been reported.<sup>7, 35</sup>

2. No undulating membrane has been definitely demonstrated in any Spirochæta. The alleged undulating membrane depicted by Perrin<sup>17</sup> and Schaudinn<sup>36</sup> in the dried preparations of certain mussel spirochætes is an artefact brought about by improper fixation; namely, the torn crista of a cristispira.<sup>20</sup>

3. The alleged chromatin rods and spirals described by Perrin in the case of certain mussel spirochetes known as Spirochæta balbianii (Cristispira of Gross) are now said to be nothing but a distorted arrangement of volutin substance or chromidial granules which under optimum fixation gather themselves along the walls of the chambered structure of the cell body.

4. The absence or presence of cell membrane seems to depend upon the variety of "spirochætes." Thus the original type organism of Ehrenberg was described as being devoid of a membrane and is still so regarded by all who have studied this organism. On the other hand the mussel spirochætes and various small parasitic species are now said to be provided with a thin but elastic membrane which cannot be differentiated from the cell body by means of staining reactions. The presence of a membrane would suggest a close affinity with Spirillum, but the latter has a stiff nonelastic membrane.<sup>22</sup>

5. In regard to the motor organ no generalization can be made. The original type organism of Spirochæta and all mussel "spirochætes" are devoid of any special motor apparatus. On the other hand, a terminal process, consisting of a delicate, elastic filament with minute, regularly set curves, may in the case of various small parasitic spirochetes be found to project from one or both ends of the body. Borrel<sup>37</sup> and Zettnow<sup>38</sup> obtained some preparations in which Spirochætes of fowl spirillosis and relapsing fever appeared to possess peritrichal flagella, but this must have been a case of artefact formation, as no one has since been able to confirm their find-

ings. Schaudinn considered the terminal process to be identical with the periplastic appendage of a flagellate.

6. Certain spirochaetes such as *S. balanitidis* and *S. buccalis*, etc., were said by Schaudinn,<sup>36</sup> Hoffmann and Prowazek,<sup>39</sup> to have a flattened, ribbon-formed body. Later investigators hold that the body is cylindrical and round on section.

7. Encystment, or the resting stage, such as observed in protozoan organisms, has been suggested<sup>17, 40</sup> as existing, but never satisfactorily proved.

It will be seen that the findings of later investigators deduct much of the foundation upon which the protozoan theory of "spirochaetes" had been based. Not only do they separate the spirochaetes from the Protozoa, but they also bring out certain new facts which make it difficult to include them among the Bacteria as was formerly done by those who opposed the view of their protozoan nature. As has been briefly remarked, the spiral organisms called spirochaetes are not of uniform structure, but according to recent investigations, fall under several great divisions. It was owing to the imperfection of the methods of study that the free living forms and numerous parasitic varieties were at one time all held to belong to the same genus. Since the introduction of dark-field microscopy,<sup>41</sup> many points which could not be satisfactorily determined with stained specimens have been carefully checked up, and the entrance into the field of certain excellent cytologists has helped to clear up many points relating to the systematic grouping of these organisms. These cytologists made extensive series of comparative studies, at the same time carefully examining the structure of bacteria, spirilla, spirulina, and oscillaria.

As has been pointed out by Bütschli,<sup>42, 43</sup> bacteria are composed of a central body and a plasmatic layer. The former contains volutin granules and some chromidial elements. The spirillum has a series of chambers, each of which is constructed like a single bacterial cell. Both are covered with a stiff cell membrane. The structure of Spirulina is similar to that of Spirillum, differing from the latter by the highly flexible character of the membrane. Now, a very similar structure was demonstrated by Gross<sup>20</sup> in the body of mussel spirochaetes and speedily confirmed by Dobell,<sup>24</sup> Zuelzer<sup>22</sup> and others. Gross, Dobell, and Zuelzer all agree that the original free-living Spirochaeta described by Ehrenberg is a unicellular organism which

bears no relation either to the mussel spirochætes or to the small parasitic varieties. This fact implies the dissociation of the long used term *Spirochæta* from those organisms which in reality were commonly known as "spirochætes." Odd as it may seem, the true *Spirochæta* has been but rarely studied, even by biologists, and certainly not to any great extent by medical men who have so much to do with the so-called "spirochætes."

Gross<sup>16</sup> was the first person who proposed to distinguish the true *Spirochæta* from the other varieties of spirochætes by creating new genera for the latter which, according to his studies, could not be classified with *Spirochæta* in the strict sense of the term. Thus for the latter type he created the name *Cristispira* (those with *Crista*), for the large parasitic "spirochætes" in fresh shell fish *Saprospira* (those without *Crista*), and the small parasitic varieties, including all pathogenic species, he designated as *Spironema*. Gross maintains that *Cristispira*, *Saprospira* and *Spironema* belong to the bacteria, and places them under the family name of *Spironemacea*. Gross<sup>44</sup> and Bosanquet<sup>32</sup> recorded a few instances in which certain mussel "spirochætes" went into spore-formation comparable to the true bacterial feature.

Dobell and Zuelzer both admit the striking resemblance between the chambered structure of *Spirillum* and *Cristispira*, but cautiously avoid accepting the bacterial theory of Gross on the ground that the last named organisms have a more elastic and flexible membrane and that they are not necessarily bacteria. Dobell, as has been stated, has proposed a new family name *Spirochætoidea* which should include not only Gross' *Spironemacea* but also *Spirochæta*. Dobell does not accept Gross' *Spironema*, as it was applied to a flagellate in 1892 (Klebs), but retains Schaudinn's *Treponema* to designate all small parasitic and pathogenic varieties. He does not consider that there is a sufficiently essential difference between them to warrant two genera. Zuelzer regards the affinity between the mussel "spirochætes" and *Spirulina* (one of the Cyanophycean genera), as being much closer than that between these types and *Spirillum*. On the other hand Gonder<sup>45</sup> accepts the classification of Gross more completely. He does not, however, share Gross' view that these organisms are definitely of a plant nature, holding that certain features indicate their partial affinity to the protozoa. He also differs from Gross in including *Spirochæta* under *Spironemacea* and in retaining

Schaudinn's term *Treponema* for the organisms of syphilis and yaws and such affections, while he accepts Gross' term *Spirochæta* for other varieties such as the "spirochaetes" of relapsing fevers, tick fever, etc. The situation is still confused.

#### CLASSIFICATION AFTER GONDER (1912)

##### SPIRONEMACEA (GROSS, 1910)

<i>Spirochæta</i> ..... (Ehrenberg, 1838)	Type: <i>Spirochæta plicatilis</i> , etc., all free living.
<i>Cristispira</i> ..... (Gross, 1910)	Type: <i>Cristispira balbianii</i> and other varieties found in mussels.
<i>Spirochæta</i> ..... (Vuillemin, 1905)	Type: <i>Spirochæta recurrentis</i> , and other parasitic and pathogenic varieties living in blood.
<i>Treponema</i> ..... (Schaudinn, 1905)	Type: <i>Treponema pallidum</i> , <i>Treponema pertenue</i> , and other varieties with closely set spirals.

#### CLASSIFICATION AFTER GROSS (1912)

<i>Spirochæta</i> ..... (Ehrenberg)	Type: <i>Spirochæta plicatilis</i> . Unicellular organism without a membrane or flagellum, highly flexible. Free living. Transverse division.
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##### SPIRONEMACEA (GROSS, 1912)

<i>Cristispira</i> ..... (Gross, 1910-11)	Including different varieties living in certain mussels. C. <i>balbianii</i> , C. <i>anodontæ</i> , C. <i>pectinis</i> , etc. All possess a crista. Chambered structure of the body. Sporulation. Transverse division.
<i>Saprospira</i> ..... (Gross, 1911)	Similar to the foregoing except that there is no crista. Found in foraminiferous sand. Sporulation. Transverse division.
<i>Spirochæta</i> ..... (Vuillemin, 1905)	Including small parasitic varieties: S. <i>pallidum</i> , S. <i>pertenue</i> , S. <i>recurrentis</i> , S. <i>gallinarum</i> , etc. Probably multicellular (or chambered.) Transverse division. Flagella or terminal thread present.

#### CLASSIFICATION AFTER DOBELL

##### SPIROCHÆTOIDEA (DOBELL) 1910-1911

<i>Spirochæta</i> ..... (Ehrenberg, 1838)	Free living forms, fresh water or marine. <i>Spirochæta plicatilis</i> (Ehrenberg) S. <i>gigantea</i> .
<i>Treponema</i> ..... (Schaudinn, 1905)	Parasitic in animals, vertebrates and invertebrates. T. <i>pallidum</i> (Schaudinn), T. <i>recurrentis</i> , T. <i>dentium</i> , etc.
<i>Cristispira</i> ..... (Gross, 1910)	Parasite in Lamellibranchiata (mussels). C. <i>balbianii</i> certes, C. <i>anodontæ</i> , C. <i>pectinis</i> , C. <i>veneris</i> .

#### CLASSIFICATION AFTER MIGULA (1897)

Bacteria .....	Coccaceæ, Bacteriaceæ, Spirillaceæ, Chlamydo-bacteriaceæ and Beggiatoaceæ.
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## SPIRILLACEÆ

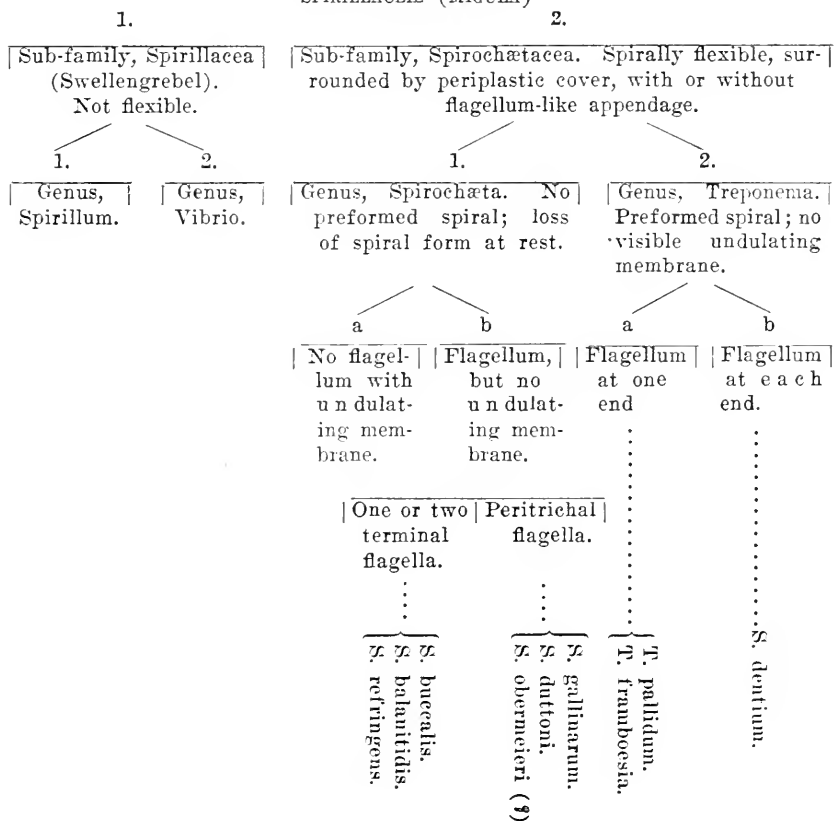
Spirosoma .....	Rigid; no organ of motion.
Microspira .....	Rigid; one seldom two or three, polar wavy flagella.
Spirillum .....	Rigid; polar tufts of 5-20 flagella, mostly semi-circular or wavy.
Spirochæta .....	Flexuous, motion organ unknown, probably an undulating membrane.

## CLASSIFICATION AFTER SWELLENGREBEL

Bacteria...	{	Spirochætaceæ.	{	More or less distinct properties of protozoa but not much more so than the bacteria capable of forming S or Fe in contrast to those producing nitrification. Plasmolysable like the Spirilla.
		Spirillaceæ		
		Coccaceæ		

## CLASSIFICATION AFTER LEVADITI (1912)

## SPIRILLACEÆ (MIGULA)



Let us consider each of the groups in some detail on the basis of a newer classification.

*Spirochæta*.—According to Schaudinn,<sup>20</sup> the type organism of *Spirochæta* possesses certain features which are also found in trypanosomes—such as an undulating membrane, periplastic fibrillar process, longitudinal division, etc. But this apparent resemblance has been shown to be erroneous. Thus, according to the latest contributions made by Zuelzer,<sup>22</sup> the original type organism, *Spirochæta plicatilis*, has no chambered structure but is provided with a straight fibrillar axial filament surrounded by a plasmatic spiral layer which covers it unequally in different places. The organism consists of a single cell. Volutin granules which can be demonstrated by certain microchemical reactions are regularly disposed within the plasmatic layer. During motion the plasmatic layer at a given position becomes thickened or reduced in volume according to the current of the substance. The spirals of the plasmatic layer surrounding the straight axial filament occur regularly and closely, while the whole body shows several irregular undulations. There is no flagellum or periplastic terminal process, and no membrane has been demonstrated. It measures 100-200  $\mu$  on an average, sometimes attaining a length of 500  $\mu$ , whereas it is only 0.5-0.75  $\mu$  in width. Unlike the other spiral organisms bearing the name of *Spirochæta* (undoubtedly indiscriminately applied) the members of this group of real spirochætes do not swim, but their locomotion is effected by a creeping movement along the surface of a supporting object. Multiplication is brought about by transverse division which is effected by a thickening of a certain part of the axial filament where a cross fissure takes place, followed by the strangulation of the plasmatic layer at the corresponding spot. Since Ehrenberg described the first species, four more species have been added, one by Contaucuzène<sup>21</sup> in 1910, and three by Zuelzer<sup>22</sup> in 1912. They are all free-living and are not known to be responsible for any pathological conditions in either human beings or animals.

Since the essential characteristics of the group of true *Spirochæta* do not agree with those of various other species hitherto unreservedly called spirochætes, the necessity of reclassification became apparent as soon as these facts were known about 1910, whereupon Gross, Dobell, and others undertook special studies in this connection. As

has been mentioned, Gross, Dobell, and Gonder all possess their individual ways of classification, but all agree on one point; i. e., that the majority of the organisms known as spirochætes are not spirochætes in the strict systematic sense and must, therefore, be differently designated. Gross was the first to do this, and he was followed by Dobell and Gonder who introduced some modifications, but it seems that the family term *Spironemacea* of Gross has found a wider acceptance than Dobell's *Spirochætoidea*, although both include practically the same constituent organisms under a slightly different generic name. Thus Dobell accepts Gross' generic names *Cristispira* and *Saprospira* (provided that this genus can be recognized by other investigators) to cover the varieties found in shell fish, while preferring to use *Treponema* instead of *Spironema* as proposed by Gross. Dobell's family *Spirochætoidea* comprehends, besides all the constituents of Gross' family *Spironemacea*, the genus of the true *Spirochæta*. Whether the segregation of *Spirochæta* from the other genera composing *Spironemacea* is justified or not seems still debatable, inasmuch as the differences between the genus *Cristispira* and the genus *Spironema* are, I believe, no less striking than those which induced Gross to separate the *Spirochæta* from them. According to personal observations on small "*Spirochætes*" there seem to exist more affinities in the structure of true *Spirochæta* and the small parasitic varieties than are assumed by Gross and other investigators. For the present I will dwell upon different groups of organisms, which those investigators have classified as separate genera, and in order to give a basis for further development of the subject, I propose to employ the new generic names proposed by Gross, without, at the same time, committing myself to his views.

*Cristispira*.—This genus was created by Gross in 1910 for the large saprophytic commensal spiral organisms found in the alimentary canal of certain varieties of shell fish. They are chiefly found in the crystalline style which is a jelly-like projection in the stomach. The most unique feature of the genus is the presence of a crista or ridge, which extends spirally along the whole length of the body, whence the name *Cristispira*. Certes<sup>47</sup> considered the type organism of the genus *Cristispira balbianii* to be a trypanosome on account of the presence of an undulating membrane (later recognized by Gross as a ridge) and it has been called *Trypanosoma* or *Spirochæta* indiffer-

ently. Laveran and Mesnil<sup>48</sup> in 1901 regarded it as allied to the bacteria. Perrin<sup>17</sup> in 1905-1906 took up the subject and arrived at the conclusion that it has many features in common with the trypanosomes. This he observed from stained preparations in which he found an undulating membrane, a spirally arranged nuclear rod, as well as various mitotic figures and longitudinal division. Perrin's observations were in part confirmed by Keysselitz,<sup>49, 50</sup> Swellengrebel,<sup>31</sup> Hoelling,<sup>27, 28</sup> Gonder,<sup>23</sup> and Fantham,<sup>29</sup> but a later investigation of Schellack<sup>19</sup> brought out an entirely different set of facts. According to Schellack the undulating membrane and spiral nuclear rod or alleged karyokinetic figures are an artefact caused by improper fixation (dry method). In properly fixed preparations the cell body is composed of an alveolar protoplasm and contains a number of transverse walls. In his later works Gonder<sup>45</sup> confirmed Schellack's observations. Zuelzer<sup>22</sup> and Dobell<sup>24</sup> found chromatin (and volutin) granules to be deposited along the surface of the transverse septa, while Gross<sup>20</sup> failed to see any chromatic granules in *Cristispira*. On the other hand, Hoelling thinks that the entire cell body is saturated with diffuse chromatin substance. The chambered structure of the cell body is regarded by Gross as a sign of the multicellular nature of the organism, but many authors hesitate to accept this view, maintaining that it is a single organism with numerous cross septa. Gross, Zuelzer, and Dobell all agree that the cell body is surrounded by a strong membrane similar to that found in bacteria, although Zuelzer distinguishes it from the latter by its high flexibility. They found that the membrane had a double contour and protected the cell body from the solvent action of various substances such as saponin as well as from acids and alkalies, a fact explained by Gonder as not necessarily due to the presence of a membrane but to the more concentrated external fibrillar layer on the cell surface. In fact, Gonder described a fibrillar appearance of the external layer of the cell body after the organism had been acted upon for some time by certain chemicals.<sup>45</sup>

Opinions still vary as to the origin of the ridge or crista. Earlier workers viewed it as an undulating membrane.<sup>17</sup> Gross, Zuelzer, and Dobell hold that it is a superposed structure having no direct connection with the cell body, while Schellack regards it as a true periplast traversed by numerous fibrils. He believes that the so-called undulating membrane of the authors of the *Cristispira* is an artefact pro-



duced by defective technic. Hoelling, as well as Fantham and Porter, entertains a view similar to that of Schellack, and the presence of a myoneme in the periplast was even maintained by Fantham and Porter. Mackinnon<sup>51</sup> and Vlès<sup>52</sup> were unable to demonstrate any myoneme in the periplast, although Borrel and Cernovodeanu<sup>53</sup> assume that there exists a myoneme in the membrane which enables it to flatten or fold the ridge. When the organism is subjected to macerating or solvent agents (saponin, acid, alkali, etc.) the membrane is first attacked. The delicate fibrils become quite distinct in the course of dissolution, but the whole structure finally disappears completely, showing the plasmatic nature of the membrane. The cell body is much more resistant.

Division is exclusively transverse, according to the investigations of Schellack, Gross, Zuelzer, Dobell, Laveran, and Mesnil, while earlier investigators (Perrin, Keysselitz, Gonder, etc.) considered it longitudinal. Fantham and Porter,<sup>35</sup> working with *S. obermeieri* and *S. duttoni*, found both modes of division occurring. It is possible that a peculiar mode of division, described by Gross<sup>20, 54</sup> as an *incurvation*, might have been the cause of mistaking it for longitudinal division. Incurvation is a phase of the transverse division of *Cristispira*, whose body first doubles up (incurvates) at the segment where the fission is to take place and then after some time completes the process. During the incurvation both halves of the organism intertwine and simulate a stage of longitudinal division.

Sporulation was described by Gross<sup>44</sup> who saw a *Cristispira* produce a series of somewhat smaller, highly refractile, oval bodies out of the square chambered structure of the cell body. These oval bodies were seen to separate into individuals, but no new *cristispira* could be made to sprout out of these bodies (or so-called spores). Bosanquet<sup>32</sup> made a similar observation. The question of sporulation is still open to further confirmation and is very important in view of the divided opinion regarding the affinity of this group in the system.

The cell body is highly flexible, round on section, wavy or spirally wound, possessing not more than three or four curves. There are neither flagella nor terminal projections, except in one small species, *C. spiculifera*, which Schellack described as having a terminal filament.

There are about 18 known species which inhabit different varieties

of shell fish belonging to nearly twelve different genera of Lamellibranchs, including common oysters and fresh water mussels. These genera are *Ostrea*, *Anodonta*, *Chama*, *Pinna*, *Maetra*, *Pecten*, *Modiola*, *Lima*, *Gastrochæna*, *Saxicava*, *Tapes*, and *Umo*. *Cristispira balbianii* and *C. anodonta* are the largest species and measure 100-130  $\mu$  in length and 3-5  $\mu$  in width, while the smallest representative of the genus, *C. papillosum*, measures but 18.5-20  $\mu$  by 1.1-1.4  $\mu$ .

*Saprospira*.—Gross<sup>20</sup> proposed to introduce this genus in order to group together a new species of mussel "spirochaetes" which distinguished themselves from *Cristispira* by the absence of a crista. Their habitat and other cytological features are the same as those noted in the *Cristispiræ*. According to this investigator, *Saprospira grandis* and *S. nana* undergo multiple transverse division and bear a more distinctly bacterial aspect.

*Spironema* and *Treponema*.—Under *Spironema*, Gross classified all the pathogenic and small saprophytic varieties. Dobell<sup>24</sup> substituted *Spironema* for Schaudinn's *Treponema* on the basis that the former term was applied to a flagellate, *Spironema multiciliatum*<sup>15</sup> by Klebs in 1892; for he did not consider it necessary to create two genera out of these organisms. Gonder still hesitates to drop the distinction between the group of "blood spirochaetes" and that of "tissue spirochaetes," the latter containing *Treponema pallidum* as type organism. While Schaudinn's original criteria for *Treponema* are no longer valid as regards several points, Gonder proposes to retain the term *Treponema* for the pallidum group and to accept *Spironema* for the more irregularly curved, wavy varieties to which most of the "blood spirochaetes" and saprophytic parasites belong. From personal observations I believe the differences between the two groups to be differences of degree, not of quality. They should belong to one and the same genus as may be seen from the characteristics enumerated below. *Spironema* and *Treponema* have a slender, cylindrical, spirally wound, highly flexible body, which exhibits serpentine, cork-screw-like, and sometimes lashing movements. The spiral curves are partially stretched and drawn together with a certain rhythm, so that an actively motile organism resembles a spiral spring which is alternately drawn out and relaxed. When reduced in motility the organism may rotate along its axis in one and then in another direction without changing its curves. In certain species a

lateral bending or swinging motion of one half of the body may be seen. It seems to be the general rule that the more active and energetic an organism is, the less rigid are its curves. On the whole the pallidum group (*Treponema*) exhibits a less energetic motility than the heavier group (*Spironema*) which it relinquishes much sooner than the latter. Therefore, it is only in perfectly fresh material (such as that obtained from an experimental syphilitic lesion in animals at the moment of examination) that the stretching of the curves, as in the case of so-called *Spironema*, can be recognized. This point can be clearly demonstrated in a section of syphiloma in a rabbit's testicle fixed immediately after removal from the animal. Here we find the organisms showing most striking irregularity of curves very unlike the accustomed picture of regularly curved specimens found in a section obtained from postmortem material, such as a tissue from macerated congenitally syphilitic fetus (Flexner)<sup>55</sup> or from a preparation made after the organism has become sluggish. The reverse is also true. A *spironema* from a case of relapsing fever is always wavy and irregularly curved in a stained preparation, but is much more regular when observed under the dark-field microscope and becomes completely regular when nearing death as a result of being exposed to progressively unfavorable conditions. In a culture where the motility is somewhat less active the organism appears just as regularly curved as a *treponema*. The sudden death of these organisms leaves them in a state of motion, hence their irregular curves.

The body of *Spironema* is much heavier than that of *Treponema* and in relation to different dyes it may be stated that the former takes on a more bluish component of Giemsa's solution than the latter, which usually takes on the red. In regard to the structure of the cell body, the minuteness of these organisms precludes the possibility of obtaining much information by means of our present methods of differentiation. Many authors assume the presence of a membrane analogous to the periplast of a flagellate and believe that it can be demonstrated by means of maceration. In one species of *Spironema*, Prowazek<sup>40</sup> assumed a central axial filament surrounded by a layer of cytoplasm. The active motility exhibited by these organisms led some investigators to suggest the existence of contractile fibrils or a myoneme in the cell body. My observations

on fresh specimens obtained from pure cultures of these organisms support the view that these *spirochates* are provided with an axial spiral filament covered with a layer of protoplasm. On the surface of the cell body there is a thin membrane which can be detected when the organism undergoes degeneration. At this stage the cytoplasm becomes so rarefied—i. e., it escapes from the space which is occupied—that the axial filament and the membrane can be easily recognized. In a subsequent phase the membrane also disappears, leaving the axial filament denuded. This is a common phenomenon in the cultivation of this group of organisms. Schellack<sup>19</sup> maintains that the external layer of the cell body stains red with iron hematoxylin eosin, while the inner layer takes on a dark bluish tint, hence the former is of ectoplasmatic and the latter of endoplasmatic origin. Gonder<sup>56</sup> describes an ectoplasmatic layer in *Spironema vesperuginis*. Fantham and Porter<sup>35</sup> as well as Prowazek<sup>40</sup> mention the existence in *Spironemata* of an undulating membrane, as was originally suggested by Schaudinn<sup>36</sup> owing to a wavy movement which he observed to travel through the body of a resting spironema. Gross and Zuelzer failed to demonstrate any such particular structure. Another important feature of *Spironema* and *Treponema* is the presence of a terminal appendage projecting from the end of the cell body. The bodies of *Spironemata* and *Treponemata* taper at both extremities from which is sent out a very fine terminal thread, at one or both ends. The length of the terminal appendage may reach  $\frac{1}{3}$  to  $\frac{1}{2}$  of the body and is immeasurably thin. In old cultures, especially when grown in a fluid medium, these terminal appendages are much heavier and more easily recognized than in a specimen derived direct from the natural habitat. The terminal filament is provided throughout its length with numerous, closely set, regular curves.<sup>57</sup> It is rigidly joined at the pointed ends of the body or sometimes in such a loose manner as to permit the joint to bend at any angle to the long axis of the organism. No proper motility can be discerned in the appendage, which is elastic. In certain specimens an active swinging or jerking movement can be seen to be transmitted by the organism, which is able to do this by means of its contractile element (myoneme?) contained within the body. In several instances in which the cultivated *Spironema recurrentis* had been exposed to the solvent action of certain chemicals

(saponin, sodium taurocholate, etc.), I have observed many denuded axial filaments (their cytoplasmic layer having been dissolved) to which the terminal filaments were also attached. Suddenly I saw some of the terminal projections commence active jerking and swinging motions. The skeletal axial filaments still remained. By means of careful examination it was found that there was a pair of highly refractile, round bodies attached to the skeletal filaments near both extremities. These bodies, which measured about  $0.5\ \mu$  in diameter, appeared to have some contractility as suggested by the alternate change in the degree of the refraction of light. Whether or not these bodies represent some sort of myonemous elements cannot be definitely stated, but it is significant that similar nodules, if not in pairs, can be seen to travel from one point to another in an actively motile spironema. Prowazek<sup>58</sup> once called attention to the phenomenon of plasmatic condensation in the body of *Spironema gallinarum*.

The nature of the terminal appendage is not known. Many authors (Hoffmann, Prowazek, etc., on *S. buccalis* and *S. balanitidis*; Novy and Knapp on *S. recurrentis*) view it as a prolongation of the periplastic fibrils which are in connection with the periplast. Others regard it simply as a drawn out part of the cytoplasm produced at the line of division. I am inclined to think that the terminal projection with regularly set curves is a separate part not directly connected with the membrane, nor existing as a prolongation of the axial filament. It is connected with the cell extremity by means of a tendinous substance. It resembles the flagellum of certain bacteria, inasmuch as it is similarly elastic, finely set with regular curves, and visible under the dark-field microscope. On the other hand, a great many of the bacterial flagella cannot be demonstrated in a fresh preparation even by means of a dark-field illumination. Zettnow,<sup>38</sup> Borrell<sup>37</sup> and Fraenkel<sup>59</sup> obtained preparations of *S. recurrentis*, *S. gallinarum* and *S. duttoni* in which peritrichal "flagella" were shown by means of flagella staining methods, but these flagella-like fibrils are now regarded as fibrils which have become detached from the external layer of the organisms through maceration. By means of the lucidol method of Szécsi,<sup>60</sup> Gonder<sup>45</sup> succeeded in staining one fine terminal projection at each end of *S. recurrentis* as did also Wolbach by the adoption of Casares Gil's<sup>61</sup> method.

There are several views regarding the mode of multiplication.

The theory most generally accepted is that these spironemata undergo transverse division like bacteria, differing from the latter, however, in not forming a wall at the point of division. The division is effected by means of a thinning out process of the protoplasma which for a time bridges the two newly formed daughter cells. Finally they separate by the severance of the connecting thread. Novy and Knapp<sup>18</sup> described a cleft formation at the point of division. The view of the transverse division is held by Koch, Novy and Knapp, Metchnikoff, C. Fraenkel, Borrel, Laveran, Sobernheim, Gross, Thesing, Schellack, Nakano,<sup>62</sup> and others. On the other hand Schaudinn, Hoffmann, Hartmann, Keysselitz, Herxheimer, Prowazek, Gonder, Fantham, and Porter support the theory of a longitudinal division as in the flagellates. Indeed, Krysztalowicz and Siedlecki<sup>63</sup> in 1905 went so far as to propose the term "Spiroflagellata" under Mastigophora. I have also observed instances in which the phenomena could only be explained by longitudinal division. Thus, in pure cultures of various spironemata and treponemata we find forms in which a longitudinal cleft can be traced in the somewhat heavier specimens. The cleft may run but a short distance, or one-third, one-half or almost the entire length of the body. In some specimens the cleft widens up and causes one-half of the body to be split into two limbs (two daughter cells in half separation). Observed under the dark-field microscope the process is seen to be slow. It may be added that it is tedious to actually follow up the entire process of any mode of division under the microscope, no matter whether this be transverse or longitudinal. As may easily be conceived, those who hold the theory of transverse division argue that the forms held by their opponents to be a stage of longitudinal division are formed by two entwined spironemata which having been produced by transverse division are still connected by a delicate plasmatic bridge. This argument, however, can also be used in the reverse sense in favor of longitudinal division, as it is also possible that the two daughter cells which have just undergone cell division can remain united at their ends, thus bearing the appearance of representing a stage of transverse division. A strong support in favor of the transverse mode of multiplication lies in the formation of a very long thread consisting of several sections united together by means of a delicate bridge between them. This phenomenon is of

common occurrence in any spironema or treponema culture. It is highly probable that the usual mode of division in culture is transverse, although the possibility of longitudinal division cannot be excluded. Recently Meirowsky<sup>64</sup> advanced the view that Spironema and Treponema besides multiplying transversely also do so by a process of fructification (Doldenbildung) and budding (Knospbildung) similar to that observed in some lower plant organisms. His ideas were chiefly based upon phenomena observed by means of various methods of vital staining, in a culture of *Treponema pallidum* (furnished by Sowade). He describes numerous granules collected in a group at one point or another along the body of the pallidum and also branching out of sprouts from some of the specimens. There are many factors to be taken into consideration in such an experimental arrangement which will make it difficult to properly estimate the value of the observations. Those made under the microscope on a preparation containing the organisms, consisting of semi-coagulated horse serum, solution of precipitable aniline dyes (effected particularly through a change of reaction in the medium) are of a disputable character when we consider the absence of strict aseptic precautions as well as the comparatively long period of observation (many days and weeks) during which a preparation had been kept for observation. It is possible that under these unfavorable conditions various forms of involution result which do not appear under normal cultural conditions. Certainly it is not convincing that this so-called fructification or budding also occurs in the body of infected hosts.

Balfour<sup>65, 66</sup> noticed the appearance of certain granules within some of the erythrocytes of fowls which had just stood the first attack of the Sudanese fowl spironematoses and thought that these granules give rise to a new generation of the spiral forms of the organisms which reappear at the second attack. That is to say, that a Spironema found by Balfour in a Sudan epizootia possesses a spiral and a granular phase of life. Leishman,<sup>67</sup> Blanc,<sup>68</sup> Fantham,<sup>69</sup> Nuttall,<sup>69a</sup> and Hindle<sup>70</sup> also entertain the belief that *Spironema duttoni* and *Spironema gallinarum* adopt a granular form under certain conditions, and that a spiral form can sprout out when the conditions become favorable. Thus in the body of infected ticks these spiral

organisms undergo segmentation and numerous granules are produced, a process analogous to sporulation. These granules were called by the authors coccoid bodies, infective granules, or spores. This view was supported by the histological studies of Hindle who secured a series of preparations in which these granules can be demonstrated in the body of the tick. According to Hindle these granules become spiral when the infected tick is incubated at 37° C. for a certain time. In contradistinction to the above findings, Marchoux and Couvy,<sup>71</sup> Gleitsmann,<sup>72</sup> Gonder,<sup>45</sup> and Todd and Wolbach<sup>73</sup> maintain that in an infected tick some motile spirochetes can always be demonstrated and that the granules described by Hindle and others are not specific for the infected ticks, but can also be found in the control specimens. Fantham<sup>69</sup> points out, however, that the granules of normal ticks are not identical with the coccoid bodies of *Spirochaeta* found in the infected ticks.

Schaudinn, Prowazek, and others noticed that certain species formed nodules under adverse conditions and suggested that these may represent a resting stage (or resistant form); but Schellack and Wolbach regard them as a depression phenomenon which can also be induced by prolonged treatment of the organisms with a saline solution. Besides, there is a peculiar, highly refractile, round body which is very often found attached somewhere along the side of the body of the organism. There may be one or more such bodies in a specimen. The significance of this body is still obscure, but it may possibly be caused through a disturbance of the osmotic equivalence existing between the cytoplasm of the organism and the medium, not unlike the phenomenon known as plasmolysis. I have demonstrated its occurrence in the cultivated specimens of various species of *Spirochaeta* and *Treponema*. The body is more frequently present in an old culture in which innumerable granules are also found. In certain culture tubes these minute granules are mostly of varying size. By making a transplant of such a culture into a new medium it was found that, when examined several days later, the new culture contained many short spiral forms which were in one manner or another intimately connected with the granules. This phenomenon suggested the possibility of representing the sprouting of the spiral forms from the granules.



## PATHOGENICITY

Spirochetes and treponemes are parasitic, and some varieties are responsible for various diseases in man and animals. Various forms of acute febrile diseases, as well as chronic pathological conditions are caused by the invasion of the blood or tissues by this group of organisms. It may be mentioned that the spirochetes are almost always transmitted from a sick individual to a normal person through the intermediary of certain blood-sucking insects and invade the blood principally, whereas the pathogenic treponemes are carried from man to man by direct contact and show a predilection for various organs and tissues. As a rule the phase of the spirochetal infection is acute and brief and that of the treponemal invasion runs a chronic course, as instanced in the former case by the type of relapsing and tick fevers and in the latter by syphilis and yaws.

Besides the pathogenic species there are a large number of saprophytic varieties belonging to these two genera (or one, according to certain classifications) which are common inhabitants of the oral cavity, genitalia, and alimentary tract of man and animals. Some forms are frequently associated with certain pathological conditions, but their etiologic significance has not been definitely determined. Such is the case with *S. balanitidis* in *Ulcus erosina circinata*, *S. vincenti* in an acute angina, *S. schaudinni* in *Ulcus tropicus* and *Treponema mucosum* in *pyorrhea alveolaris*, etc. It may be that some of these play the role of a secondary invader and aggravate the conditions.

In the following table, I have enumerated the different species of Spirocheta and Treponema which have hitherto been observed by various investigators throughout the animal kingdom. It will be seen that the search has been more thorough in the case of the warm-blooded vertebrates than the cold-blooded orders, while even mosquitoes, ants, mites, and fleas are found to harbor certain species of these organisms.

## SPIROCHÆTÆ (LARGE FREE-LIVING FORMS)

Sp. plicatilis.*	Fresh water. 100-200 $\mu$ , 500 $\mu$ max. $\times$ 0.5-0.75 $\mu$ Ehrenberg, 1838.
Sp. plicatilis marina*	.....Zuelzer, 1912.
Sp. plicatilis eurystrepta*	.....Zuelzer, 1912.
Sp. stenostrepta*	.....Zuelzer, 1912.
Sp. daxensis†	.....Hot spring. 30-100 $\mu$ $\times$ 0.5-0.75 $\mu$ Cantacuzene, 1910.

\*Zuelzer cultivated these varieties in a suitable medium and proved each of them to be different from the others; hence she made subspecies. Schaudinn considered them to represent male and female forms.

†In the water of hot springs of Dax (52°-56° C.).

## CRISTISPIRÆ AND SAPROSPIRÆ (LARGE SAPROPHYTIC AND COMMENSAL FORMS IN THE ALIMENTARY CANALS OF SHELLFISH)

- Cristispira balbianii*\*. *Ostrea angulata*  
*O. edulis*.....100-120 $\mu$ ×3-5 $\mu$ . Certes, 1882.  
*C. anodontæ*..... Fresh water mussel,  
*A. cygnea*; also  
*A. mutabilis*. 130 $\mu$ ×3-4 $\mu$ .....Keysselitz, 1906.  
*C. spiculifera*..... ditto .....28-36 $\mu$ ×0.7-1.1 $\mu$ . Schellack, 1909.  
*C. primæ*†..... *Prima squamosa*,  
*P. nobilis* .....10-60 $\mu$ ×0.5-3 $\mu$  ....Gonder, 1908.  
*C. mactræ*..... *Maetra sulcataria* 45-70 $\mu$ ×0.8-1.0 $\mu$ ...Prowazek, 1910.  
*C. pectinis*..... *Peeten jacobæus*...72 $\mu$  ×1.5 $\mu$  .....Gross, 1910.  
*C. interrogationis*.....25 $\mu$  ×0.5 $\mu$  .....Gross, 1910.  
*C. veneris*..... *Venus casta* .....Dobell, 1910.  
*Saprospira grandis* .....Gross, 1912.  
*S. nana* .....Gross, 1912.

\*Once considered to be trypanosome or spirochæta.

†Bosanquet doubts its being a separate species from *C. anodontæ*.

††Gonder once described a blepharoplast near one blunt end; nucleus in single rod or irregular masses. Specimens with rod-formed nucleus may be male elements, since they are highly active, the others female or indifferent elements. A concentration of all the chromatin into one rounded mass was sometimes observed. Encystment also occurs. Gonder no longer upholds his above-cited interpretations, explaining them on the ground of faulty technical handling of the preparation.

(SHELLACK)		Length		Length		Ends
		Aver- age	Ex- tremes	Aver- age	Ex- tremes	
<i>C. balbianii</i> .....	<i>Ostrea edulis</i> ....	39	35-42	1.3	1.1-1.5	Rounded, no t. ap.
<i>C. ostræ</i> .....	<i>Ostrea edulis</i> ....	41.5	38-42.5	1.1	1.0-1.3	Sharp, no t. ap.
<i>C. chamæ</i> .....	<i>Chama gry- phoides</i>	45.6	45-46.5	1.4	1.3-1.5	Rounded, no t. ap.
	<i>Ch. sinistrorsa</i>					
<i>C. anodontæ</i> .....	<i>Anodonta mut- abilis</i>	46	39-50.5	1.0	0.9-1.2	Rounded, no t. ap.
<i>C. spiculifera</i> ....	<i>Anodonta</i> .....	33	28-36.5	0.9	0.7-1.1	Pointed, t. filam.
<i>C. modiolæ</i> .....	<i>M. barbato</i> .....	37.5	36-40	0.8	0.7-0.9	Rounded, no t. ap.
<i>C. primæ</i> .....	<i>P. nobilis</i> .....	30.4	29-31	1.0	0.8-1.1	Rounded, no t. ap.
<i>C. limæ</i> .....	<i>L. inflato</i> , <i>L. hiano</i> .	37	35-41	1.4	1.0-1.8	Rounded, no t. ap.
<i>C. cardii papillose</i>	<i>C. papillosum</i> ....	19.1	18.5-20	1.2	1.1-1.4	Rounded, no t. ap.
<i>C. tapetos</i> .....	<i>T. decussata</i> ....	34.5	29-35	1.3	1.1-1.4	Rounded, occa- sional t. ap.
<i>C. acuminata</i> ....	<i>Tapes lata</i> .....	37	43.5-49.5	1.0	0.9-1.1	Pointed, no t. ap.
<i>C. saxicavæ</i> .....	<i>Sax. aretica</i> .....	31	30-32	1.7	1.6-1.8	Rounded, no t. ap.
<i>C. gastrochænæ</i> ...	<i>G. dubia</i> .....	29	constant	1.2	1.1-1.3	One end blunt, one sharp, no t. ap.
<i>S. pusella</i> *.....	<i>Anodonta</i> , <i>Umo</i> , <i>Lima</i> , <i>Tapes</i> , etc.	13	12-14	..	0.3-0.4	Sharp pointed.

\*Bosanquet found a spirochæta 10-12 $\mu$  in length which he thinks may be identical with *Spirochæta hartmanni* of Gonder or with *S. pusella* of Schellack. No crista?

## SPIRONEMA

- S. obermeieri*\* .... Man, Europe....  $8-16\mu \times 0.25\mu$ . Cohn, 1877.<sup>74</sup>  
*S. carteri* ..... Man, India.....  $8-16\mu \times 0.2\mu$ .. Mackie, 1907.<sup>75</sup>  
*S. duttoni* ..... Man, W. Africa.  $16-30\mu \times 0.2\mu$ .. Novy and Knapp, 1906, Breinl, 1906.<sup>76</sup>  
*S. kochi* ..... Man, East Africa..... Schellack, 1907.<sup>77</sup>  
*S. berbera* ..... Man, Algiers.....  $12\mu$ .. Sergeant, 1908.<sup>78</sup>  
*S. ægyptica* ..... Man, Egypt.....  $13.5\mu$ ..  
*S. novyi* ..... Man, North America....  $12\mu$ .. Schellack, 1907.<sup>77</sup>  
*S. ieterohemor-*  
*rhagiæ*..... Man,  $4-9\mu \times 0.3\mu$ , exceptionally  
 $25\mu$ .. Inada, 1914-15.<sup>79</sup>  
*S. nodosum* ..... Man ..... Huebener and Reiter, 1916.<sup>80</sup>  
*S. gallinarum*† ... Fowl ..... Marchoux and Salimbeni, 1903.<sup>81</sup>  
*S. anserina* ..... Goose ..... Sacharoff, 1890.<sup>82</sup>  
*S. theileri* ..... Cattle,  $20-30\mu \times 0.25-0.33\mu$ .... Lãveran, 1902.  
*S. bovis cafferis*... Cattle ..... Nuttall, 1910.  
*S. equi* ..... Horse ..... Novy and Knapp.  
*S. equina* ..... Horse ..... Theiler, 1906.<sup>83</sup>  
*S. ovina* ..... Sheep ..... Blanchard, 1906.  
*S. macaci* ..... Inacacus, Ceylon ..... Castellani and Chambers, 1908.  
*S. pitheci* ..... *Cereopethicus pates* ..... Thiroux and Dufongéré, 1910.  
French Sudan .....  
*S. lutræ* ..... Otter ..... Prowazek, 1907.  
*S. lovati* ..... Grouse's cœcum  $16-35.5\mu \times$ ... Fantham, 1910.  
*S. vesperuginis* .. Tunisian bat.  $12-18\mu \times 0.25\mu$ ... Gonder, 1908.  
*S. lagopodis* ..... Grouse's blood....  $10-18\mu \times$ ... Fantham, 1910.  
*S. laverani* ..... Mouse ..  $1.8-3.75\mu \times 0.1-0.2\mu$ .. Breinl and Kinghorn, 1906.<sup>84</sup>  
*S. suis* ..... Pigskin lesion or tumor  $6-12\mu$ . Dodd, 1906, Cleland, 1906.  
*S. muris* ..... Rat .....  $3-7\mu \times 0.2\mu$ . Wenyon, 1906.<sup>85</sup>  
*S. minor* ..... Rat .....  $5-9\mu$  ..... Carter, 1887.<sup>86</sup>  
*S. microgyratum*. Ulcerated cancers,  $5-11\mu \times$   
 $1.5-2\mu$   $2.5-6\mu \times 0.16-0.25\mu$ .... Löwenthal, 1906.<sup>87</sup>  
*S. eugyratum* .... Human intestine, stenogyr.  
 $4.6-7.7\mu$ . Werner, 1906.  
*S. stenogyratum*.. Human intestine,  $3.6-6.7\mu$ .... Werner, 1906.  
*S. gondii* ..... Rodent *Ctenodactylus gondi*  
 $16-19\mu \times 0.3\mu$  ..... Nicolle, 1907.  
*S. gadi*.... S. W. Fish, *Gadus minutus*.....  
 $10-16\mu \times 3.5-4\mu$  ..... Neumann, 1909.  
*S. pelanchysis*  
S. W. *Pelamys sarda*..  $9-10\mu \times 1-1.9\mu$ . Neumann, 1909.  
*S. jonesii*, F. W.. Fish, *Clavias angolensis*  
 $18\mu \times 0.1\mu$  ..... Dutton, Todd and Toby, 1906.  
*S. hartmanni* .... Prima squamosa,  
*P. nobilis* intestine  $6-14\mu \times 1\mu$ . Gonder, 1908.<sup>88</sup>  
*S. bufonis* ..... *Bufo vulgaris* Rectum  
 $8-10\mu \times 1.5\mu$  ..... Dobell, 1908.

## SPIRONEMA (CONT'D)

- S. minei* ..... Work. Ants. *Termes lucifugus*  
15-50 $\mu$   $\times$  0.3-1 $\mu$  ..... Prowazek, 1910.
- S. glossinae* ..... Tsetsefly stomach 8-15 $\mu$  ..... Novy and Knapp, 1906.
- S. culicis* ..... Guat. aliment. canal large ..... Jaffé, 1907.
- S. buccalists*† ..... 12-20 $\mu$   $\times$  0.5- $\mu$ . Cohn, 1877.
- S. vincenti* ..... Pharyngitis ..... 10-40 $\mu$ .. Blanchard, 1906.<sup>90</sup>
- S. gracilis* ..... Abscess near jaw ..... Vesprémi, 1907.<sup>91</sup>
- S. schandinni* .... Tropical ulcer ..... Prowazek, 1907.<sup>92</sup>
- S. pseudopallidum*. Various ulcers ..... Mulzer, 1905.<sup>93</sup>
- S. bronchialis* ... Bronchitis in Ceylon 15-30 $\mu$ .. Castellani, 1907.<sup>94</sup>
- S. phagedenis* ... Phagedenic ulcer in man .... Noguchi, 1912.<sup>95</sup>
- S. refringens* ..... 8-12 $\mu$   $\times$  0.33 $\mu$ . Schaudinn, 1905.<sup>6</sup>
- S. balanitidis* ... Balanitis .... 8-12 $\mu$   $\times$  0.5-0.75 $\mu$ . Hoffmann and Prowazek,  
1906.<sup>39</sup>
- S. obtusum* ..... Yaws lesion ..... Castellani, 1905.<sup>96</sup>
- S. acuminatum* .. Yaws ..... Castellani, 1905.<sup>96</sup>
- S. aboriginalis* ... Ulcerative granuloma on  
pedenda ..... 18-20 $\mu$ . Cleland, 1909.<sup>97</sup>
- S. interrogans* ... Yellow fever ..... 14 $\mu$   $\times$  0.17 $\mu$ . Stimson, 1909.
- S. hyos* ..... Hog cholera ..... King, Hoffmann, Bæslæck,  
1913.<sup>98, 99, 100</sup>
- S. grassi* ..... Termite in Italy ..... Doflein.
- S. termitis* ..... Termite in Ceylon large ..... Dobell, 1910.
- S. etenocephali* .. Dog flea ..... Patton.

\*Synonymous with *S. recurrentis*, Lebert, 1874.

†There are three subspecies: *S. granulosa* penetrans, in Sudan; *S. nicolleti* in Tunis, and *S. nevuxi* in Senegal.

††Subspecies: *Undulata* and *inequalis*.

Lingard described *Spironema* in the blood of the camel, dog, elephant and horse; James, in an ulcer of the dog's muzzle, and Lueet in the gastro enteritis; Mathias and Leger in the blood of the zebra and antelope; Bell and Ruquet in the stomach of a normal dog; Dobell in *Tropidonotus stolatus*; Mühlens and Gleitmann in the boa constrictor; Ed. and Ét. Sergent in the alimentary tract of *anopheles maculipennis* larva; Mühlens often found spirochaetes resembling *S. recurrentis* in the *Culex* mosquitoes.

## TREPONEMA

- T. pallidum* ..... Syphilis ..... 6-14 $\mu$   $\times$  0.2-0.25 $\mu$ . Schaudinn and Hoffmann,  
1905.<sup>6</sup>
- T. pertenu* ..... Yaws ..... Castellani, 1905.<sup>101</sup>
- T. microdentium* ..... 3-12 $\mu$   $\times$  0.2-0.25 $\mu$ . Noguchi, 1912.<sup>102</sup>
- T. dentium*† ..... Koch, 1877.
- †Subspecies: *S. recta*, *S. tenue*, *S. denticola*.
- T. macrodentium* ..... 6-18 $\mu$   $\times$  0.3-0.5 $\mu$ . Noguchi, 1912.<sup>102</sup>
- T. mucosum* ..... Pyorrhea alveolaris  
3-12 $\mu$   $\times$  0.2-0.25 $\mu$ . Noguchi, 1912.<sup>103</sup>
- T. calligrum* ... Condyloma ..... Noguchi, 1912.<sup>104</sup>

The foregoing list may be classified according to the habitat of the organisms. Thus, when they multiply within the blood circulation of man or animals they may either lead to a grave pathological condition or may produce no appreciable disturbance of the host that harbors them. In the case of certain tissue-invading species, serious pathological consequences may ensue or the host may remain more or less indifferent to the parasite.

### 1. Varieties which invade the blood principally.

(A) *Those which cause characteristic fevers known as relapsing or tick fever (pathogenic).*—There are seven for man, five for mammals and, at least, two for birds. These are:

*For man:* *Spironema obermeieri* (in European relapsing fever), *S. carteri* (in East Indian relapsing fever), *S. duttoni* (African tick fever), *S. kochi* (in East African tick fever), *S. novyi* (in American relapsing fever), *S. aegyptica*, and *S. berbera* (in Egyptian and North African relapsing fever).

*For mammals:* *Spironema theileri* (in South African cattle fever), *S. equi* and *S. equina* (in horse), and *S. ovinae* (in sheep), *S. macaci* and *S. pitheci* (both in East Indian monkeys).

*For birds:* *Spironema gallinarum* (in South American and African chicken fevers), *S. anserina* (in goose fever).

(B) *Those which do not seem to produce any grave condition, but are incidentally found (nonpathogenic).*—

*For man:* None.

*For mammals:* *Spironema lutrae* (in otter), *S. gondii*, *S. vesperuginis* (Tunisian bat), *S. muris*, *S. minor* (both in rats), *S. laverani* (in mouse). The organism found by MacNeal<sup>105</sup> may be identical with *S. muris*.

*For birds:* *Spironema lagopodis* (in grouse's blood).

*For reptiles:* *Spironemata* found in *Tropidonotus* and *Boa*.

*For fish:* *Spironema gadi*, *S. pelamydis*, *S. jonesi*.

### 2. Varieties which invade the tissue principally.

(A) *Those which cause characteristic lesions and symptoms (pathogenic).*—In this group there are no *Spironema*, but the only two known varieties belong to *Treponema*. No pathogenic tissue parasite belonging to *Spironemaceae* was found in animals. The two pathogenic *treponemata* for man are *Treponema pallidum* (in syphilis), and *T. pertenue* (in yaws).

(B) *Those which do not seem to cause any noticeable lesion.*—To this belongs a *Spirocheta* (or *Treponema*) discovered by Gaylord<sup>106, 107</sup> and Borrel<sup>108</sup> in mouse cancers. Similar organisms were found by Tyzzer,<sup>109</sup> Deetjen,<sup>110</sup> and Mezinescu.<sup>111</sup>

3. Varieties which invade both the blood and the tissues indifferently.

*Spirocheta* (?) *icterohemorrhagica* (in Weil's disease prevalent in Japan) and *S. nodosum* (in Weil's disease prevalent in Germany) are the only ones so far known to come under this heading. The former, first discovered by Inada, is probably identical with *S. nodosum* of Huebener and Reiter, who also found it independently of Inada a year later. Stokes confirmed the work of Inada on the cases prevalent in Flanders.\*

4. Varieties which may be associated with certain pathological conditions and some of which are regarded as having a more intimate relation to the lesion than that of mere secondary invaders.

There are about seven *Spirochetes* and one *Treponema* which have been recorded in man and may be included in this category. These are: *Spirocheta vincenti* (acute pharyngitis), *S. schaudinni* (in tropical ulcers), *S. bronchialis* (in pulmonary gangrene), *S. balanitidis* (*Ulcus erosiva circinata*), *S. gracilis* (ulcerating jaw), *S. aboriginalis* (ulcerative granuloma), *S. phagedenis* (in phagedenic ulcer). The only *Treponema* which may be constantly associated with pyorrhea alveolaris is *T. mucosum*. *S. suis* was found in the ulcerating lesions of pigs.

5. Varieties which are found in or about the body cavities, alimentary tract, and genitalia are nonpathogenic and numerous.

For man there are described eight species of *Spirocheta* and five species of *Treponema*. Some of them have been known for many years while others are of recent addition. It may here be noted that similar flora are encountered in mammalian animals. These are as follows:

*Spirocheta refringens*, *S. microgyratum*, *S. buccalis*, *S. acuminatum*, *S. obtusum*, *S. pseudopallidum*, *S. eugyratum*, *S. stenogyratum*, and *Treponema macrodentium*, *T. medium*, *T. microdentium*, *T. dentium*, *T. calligram*.

*S. hyos* discovered by King and Bæslack<sup>98</sup> in the blood of pigs suf-

\*Personal communication from Dr. Adrian Stokes, Captain R. A. M. C.

fering from hog cholera is considered by them to be the cause of this disease,<sup>99, 100</sup> This organism should be more extensively studied, particularly in its relation to various spirochætes found in certain conditions in this animal.<sup>112, 113</sup>

The *Spironema* flora in birds, reptiles, fish and amphibia is practically unexplored, but we find one *Spironema bufonis* in a toad.

For insects there are on record several spironemata; namely, *S. culcis* (culex mosquito), *S. termitus*, *S. grassi* (both in mites), *S. ctenocephali* (in dog fleas).

Before leaving this chapter it may be well to dwell somewhat more extensively on the two recently discovered pathogenic spironemata. Brief mention has been made of the one, namely, Inada's *S. ictero-hemorrhagæ*, causing Weil's disease. The other, discovered by Futaki, Takaki and Taniguchi<sup>114</sup> in the blood and glandular tissues in two cases of rat-bite fever in Japan, is a *Spironema* believed by them to be allied to *S. recurrentis*.

Since Weil<sup>115</sup> called attention to the existence of an infectious disease characterized by a sudden onset, chills, high fever, muscular pains, jaundice, occasional hemorrhages in the skin, and acute nephritis, there have appeared numerous contributions to establish the entity of the disease. It has been found to break out among the soldiers in a barrack or among butchers or sewage-drainers. The mortality in European epidemics was rather low (about 15 per cent). The disease reaches its maximum on the 9th or 10th day, and then gradually ends in a lysis which retards the recovery of health for about a month or longer. Death occurs before the end of the second week of the illness. A similar disease has been known in Japan for the past several years. It was reported in certain districts (Kiushiu, Chiba, Shikoku) to have claimed many thousands of victims every year among the farmers, miners, and other laborers. Children under ten years of age are seldom affected, while those who are more occupied in field work contract the disease more frequently. There seems to be no authentic instance in which the disease was carried to another individual by direct contact. While many bacilli and cocci had been isolated and temporarily held to be the causative agent of this disease, no conclusive evidence had been adduced to support them. Jaeger<sup>116</sup> once described a *B. proteus fluorescens* as the cause of Weil's disease, prevalent in 1892.

Since 1912 Inada and his associates<sup>79</sup> have undertaken an extensive experimental study of this disease, and in 1914 succeeded in transmitting it to guinea pigs. Macaeus, rabbits, rats and mice were partially or completely refractory to the inoculation. The most important points of the work of these investigators are (1) the reproduction of the typical symptoms (fever, jaundice, acute nephritis, swelling, and fatty degeneration of the liver, generalized hemorrhage, subnormal temperature before death, etc.); (2) the fact that successful inoculation of the guinea pig depends upon the period of the disease at which the blood was drawn from the patient; namely, no positive result was obtained with material taken after the first week of illness; and (3) the discovery of the Spirochæta, *S. icterohemorrhagiæ* in the blood, visceral organs, glands, affected skin, and muscles, both in man and the experimentally infected guinea pig.

It must be mentioned that the discovery of the Spirochæta was first made early in 1915 with the tissues and blood of the guinea pig, as the organisms are more abundant in experimental Weil's disease than in human cases. In October, 1915, an opportunity was afforded me to observe a number of cases of this disease occurring in Chiba and, through the cooperation of Dr. Miyajima, some material for experimental studies was collected. One of the patients had had the attack a month previously and was at the convalescent stage. He was anemic, thin, and moderately jaundiced. The urine (dark, turbid) was collected and inoculated into the peritoneal cavity of the guinea pig. The animal started to show the typical symptoms (fever, jaundice, epistaxis, petechia, bile pigment in the urine, etc.,) within one week and was examined just before death. The heart's blood showed *S. icterohemorrhagiæ* in moderate numbers. They were motile (their curves were irregular and showed lateral twitching motions or some serpentine movements). Their length varied from 9  $\mu$  to 12  $\mu$  and the width was about 0.4  $\mu$ . More organisms were seen in the emulsions of the liver and kidney. Some of the specimens were as long as 16  $\mu$  and some as short as 4  $\mu$ . The number of curves varied from 4 to 10. Inada, Ido and Iloki, and others state that the body of the organism seems to be beaded when examined under the dark-field microscope. Like other minute treponemata or spirochætata, the unstained Spirochæta of Weil's disease is invisible under the ordinary microscope. When stained with the Giemsa, carbol fuchsin, gentian



violet, or Fontana stains, the organism presents a spiral thread possessing only a few large curves with pointed extremities. There is a certain resemblance to Vincent's Spirochæta, although it is somewhat smaller and finer than the latter. A flagellum has not been demonstrated, but in a preparation stained according to the modified Fontana method,\* I was able to see a delicate projection drawn out of the pointed end of the organism. Probably there is a terminal thread. It is quite astonishing, however, to find that the organisms stained by the Levaditi method appear to be very heavy, irregular forms with a few tortuous bends and blunt ends. By applying a modified technic<sup>117</sup> the organisms stain much more elegantly and preserve their delicate appearance.

As will be mentioned later, the *Spironema icterohemorrhagiæ* has been successfully grown on artificial media and the disease reproduced in the guinea pig by means of the pure culture.

Huebener and Reiter<sup>50</sup> reported early last year (1916) that they were also able to find a Spirochæta in the experimental Weil's disease in the guinea pig. The Spirochæta, designated *S. nodosa* by them, seems to be identical with the strains isolated by the Japanese investigators. As briefly referred to, Stokes has just isolated the same organisms for the Weil's disease existing in Belgium. He also succeeded in reproducing the typical disease in guinea pigs in which the organisms were demonstrated in abundance.

The report of Futaki and his associates on the finding of a spironema in the inflamed skin and lymph glands in two cases of rat-bite fever† is interesting, inasmuch as the clinical feature of this disease had already suggested to Crohn<sup>118</sup> its possible relation to recurrent fever. Hata and others had found an effective therapeutic agent in salvarsan and mercury. These spironemata were found to be actively motile when examined by the dark-field microscope, and were successfully transmitted to the Inus monkey, guinea pig, and white rat for many generations. The organism discovered by Futaki appears to be allied to the blood spironemata of relapsing fevers. In the meanwhile

\*Fix air dried film in (1) a mixture of acetic acid 8 c.c., formalin 20 c.c., and distilled water 100 c.c. for a few minutes; rinse off the fixing reagent. Cover the film with (2) a mixture of 20% of tannin plus 1% phenol, and steam it over a flame for one minute; wash the film well and then immerse the slide in a 0.25% silver nitrate solution for a minute or two. After washing, cover the film once more with (2) and steam it over a flame, wash and dry.

†Symptoms: Incubation of 10 to 27 days, then chills, fever, headache and malaise. Local inflammation at the site of bite; pains in the limbs of the affected side; dark red eruptions and swollen lymph glands; 3 to 7 days fever with an afebrile interval of 2 to 3 days. Temperature curve similar to that of relapsing fever.

this will raise an interesting question in regard to the possible existence of a spontaneous *Spironema* infection in rats. So far as I am aware, there is no observation on record of the finding of any pathogenic *Spironema* in the rat, notwithstanding the fact that this animal had been much hunted and examined by health officers for the plague bacilli, thus affording numerous opportunities to make an accidental discovery. Perhaps the finding of Futaki may open up a new field wherein to search for a hitherto undiscovered source of disease communicable to man.

#### VIABILITY

There is a great deal of experimental data bearing upon the viability of various spiral organisms generally, especially upon the most widely investigated species, *Treponema pallidum*. In recording the results it is necessary to make a distinction between experiments made with uncultivated organisms and with those which have already adapted themselves to the artificial cultural conditions, in view of the fact that the latter offer a much greater resistance to certain external influences.

The free living *Spirochæta* lives for about a week or ten days when taken out of its natural habitat and placed in a vessel without the observance of any special precautions. On the other hand, Zuelzer<sup>22</sup> was able to keep various free living species of *Spirochæta* (plicatilis type) alive for an indefinite period of time by keeping them in a hermetically sealed vessel in which a sufficient amount of hydrogen sulphite and certain organic matters derived from stagnant water were supplied from time to time; in other words, in a culture.

The maximum time during which *Cristispira* can be kept alive is about two days even under favorable conditions. No culture has yet been obtained with any member of the shell fish parasites.

For *Spironema* it was found that the pathogenic varieties, including *S. recurrentis*, *S. duttoni*, *S. novyi*, *S. gallinarum*, still remain infective after a little more than 40 days when kept in a refrigerator (2°-4°C.).<sup>18</sup> At body temperature (37°C.) complete disintegration of the organism takes place within 48 hours. No accurate data can be found regarding the saprophytic species which, it may be assumed, can remain alive much longer than their pathogenic congeners.

Of the *Treponema* group, *Treponema pallidum* has received most

attention. Authors agree that the syphilis organism quickly becomes sluggish after being removed from the living tissues and that motility can seldom be detected in any specimen which has been maintained at 37°C. for 24 hours. On the other hand, the pallidum contained in a resected tissue (for example, a piece of chancre or rabbit's testicular syphiloma) is still found to be infective after being kept at room temperature or in a refrigerator for 48 hours or sometimes even 72 hours.\* In a culture medium consisting of rabbit's plasma, a piece of rabbit's kidney and ascitic fluid, many pallida introduced in the form of an emulsion of rabbit's testicular syphiloma remain quite active for 3 or 4 days when kept at 37°C. under anaerobic conditions. But they do not always multiply to form a real culture. It was found that postmortem material containing *Treponema pallidum* may still be able to infect a susceptible animal when inoculated within 24 hours.<sup>119</sup> The organism is killed at a temperature between 50° and 55° C. maintained for twenty minutes.

The resistance and viability of cultivated strains of *T. pallidum* is much greater than that of the organisms found in the tissues. Akatsu, working in my laboratory, found that when the pallidum is isolated from a fluid culture and put in a fraction of a cubic centimeter of the same fluid, it invariably dies within 24 hours, no matter whether it be kept at 37°, 15°, or 2°C., but it survives for 5 days at 37°, 7 days at 15°, and 10 days at 2°C. when kept in 2 c.c. of the fluid. On the other hand, a small portion of a solid culture set aside in a tube remains capable of transplantation into a new medium for 48 to 72 hours at 15°C. and for 4 to 5 days at 2°C. In a quantity of about 2 c.c. of the culture, the organism remains alive as long as twenty days.

In undisturbed cultures *T. pallidum* remains alive for a considerable length of time. Thus a solid culture, set up according to the original method<sup>120</sup> will remain transplantable to a new medium for a period of one year uninterruptedly kept at 37°C. At 15°C. it remains alive after standing 4 or 5 months, while in a refrigerator (2°C.) it survives about 2 months. In a fluid medium consisting of ascitic fluid and a piece of fresh rabbit's kidney covered with fluid paraffin, the organism lives about 2 to 3 months, and in a double tube method<sup>121</sup> about 4 months at 37°C.

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\*Isolated specimens die within ten hours in a refrigerator (Neisser).

*T. calligyum*, *T. mucosum*, *T. microdentium* are about the same as the pallidum in regard to their resistance and viability. These organisms resist the action of the sun's rays when exposed directly for several hours (4 hours and 30 minutes) at a temperature of 30°C. (summer) and 4°C. (winter), although no growth was obtainable with material exposed for 12 hours (Akatsu).

Drying promptly kills them, that is, no growth can be obtained by transplanting the dried cultures into new media.

The thermal death points for *T. pallidum* as tested out with pure cultures are as follows:

	5 min.	10 min.	15 min.	30 min.	60 min.
45° C.	+	+	+	+	+
50° C.	+	+	+	+	+
55° C.	+	+	—	—	—
60° C.	—	—	—	—	—
65° C.	—	—	—	—	—

The above data were obtained by Akatsu and closely agree with those obtained by Bronfenbrenner,<sup>122</sup> who found that the several strains of *T. pallidum* were destroyed at slightly lower temperatures. It must be stated that Bronfenbrenner used isolated organisms suspended in saline or ascitic fluid, while Akatsu subjected them to the action of heat in a thin culture tube.

#### MICROCHEMICAL REACTION

As mentioned elsewhere, a number of substances have been found to exert a dissolving or disintegrating action upon so-called "spirochaetes" in general as well as upon certain protozoa. This phenomenon is claimed by certain authors to be decisive enough to place the spirochaetes among protozoan organisms, as the majority of bacteria (pneumococcus is an exception) remain unaffected, and some can multiply freely in a saponin solution which destroys spirochaetes. While a too far-reaching generalization from these observations may be avoided, these reagents nevertheless furnish us with an excellent means of studying the microchemical structure of the organisms. The following table contains a summary of all available data which, however, is very fragmentary and incomplete.

TABLE I

	TREPONEMA PALLIDUM	SPIRONEMA RECURRENTIS	CRISTISPIRA ANODONTÆ	SPIROCHÆTA PLICATILIS
Saponin .....	10 per cent solution: 30 min., immobilized, irregular, paler. 1 hour: mostly broken up. Kills in 1:75,000 dilution.	Like pallidum when treated in 10 per cent solution.	10 per cent solution: 1-2 hours. crista fibrillar, and then indistinct.	10 per cent solution: still motile in 30 min.; longer contact makes the body shadowy, but no dissolution.
Sodium taurocholate	10 per cent solution: like the above; kills in 1:2,500 dilution.	10 per cent solution: immobile in 15 min. The outer layer shrinks into irregular masses exposing axial filament. Final disintegration.	10 per cent solution: destroyed in 15 minutes.	Same as saponin.
Sodium glycocholate	Same as sodium taurocholate.			
Sodium cholate	Same as above, but kills in 1:5,000 dilution.			
Sodium oleate.	10 per cent solution: Same as above, kills in 1:70,000 dilution.	Almost dissolved in 1 hour, but some may still be motile.		
Cobra lecithid.	Kills in 1:1,000 dilution.			
Cobra venom..	Kills in 1:1,000 dilution.			
Pepsin (0.1 in 150 c.c. of 0.3 per cent HCl)	Cells swell up in 2 hours.	.....	Slight change.	Granules appear in 2 or 3 days at 40° C., but only slight change at lower temperature.

TABLE I—(CONT'D)

	TRYPONEMA PALLIDUM	SPIRONEMA RECURRENTIS	CRISTISPIRA ANODONTÆ	SPIROCHÆTA PILICATILIS
Trypsin (0.2 in 10 c.c. of 0.5 per cent $\text{Na}_2\text{CO}_3$ )	Resist the tryptic digestion for many days.	.....	Crista, chambers and contents disappear in 24-48 hours. Membrane resistant.	Granules and axial filament made distinct in short contact. At 40° C., for 2 or 3 days, only the axial filament remains. It may break into many pieces corresponding to curves.
$\text{H}_2\text{SO}_4$ , .....	1 per cent solution: Immobilized immediately, shortened, granular, swollen, indistinct curves. 1 hour the same. 30 per cent solution: dissolves the organisms.	1 per cent solution: complete immobilization; many appear thinner, but forms well-preserved. 30 per cent solution: dissolution.	30 per cent solution dissolves them.	1 per cent solution causes immediate stretching of curves, which resume their winding when adding 1 per cent KOH, or vice versa. This can be repeated many times. 30 per cent solution dissolves the spirochæta.
KOH .....	10 per cent solution: rendered indistinct in 30 min.; dissolution in 1 hour.	10 per cent solution: dissolves most of them in 1 hour; more resistant than the pallidum.	1 per cent solution destroys Crista, membrane resists 10 per cent, but dissolved in 30 per cent with heat.	1 per cent solution dissolves granules. 2-30 per cent destroy spirochæta, axial filament most resistant. Treatment with absolute alcohol accelerates the dissolving power of KOH

TABLE I—(CONT'D)

	TREPONEMA PALLIDUM	SPIRONEMA RECURRENTIS	CRISTISPIRA ANODONTÆ	SPIROCHÆTA PLICATILIS
Na <sub>2</sub> CO <sub>3</sub> .....	1 per cent solution: immobilized, but no morphological changes.	1 per cent solution; immobilized, slightly granular, but well preserved.	.....	1 per cent solution: no effect on plasma, dissolves granules.

As will be noticed in Table I, certain reagents demonstrate the existence of a resistant membrane in *Cristispira*, a trypsin resistant axial filament in *Spirochæta*, and a shadowy sheath (?) as well as an axial spiral filament in *Spirochæta* and *Treponema*. As in the case of *Spirochæta*, no true dissolution of *Spirochæta* (both *gallinarum* and *recurrentis*) or *Treponema* was affected by the saponin, but after several hours' contact they were shrivelled and broken up into irregular pieces.

*Resistance to Disinfectant and Chemotherapeutic Agents.*—Attempts to determine the resistance of various "spirochætes" are not lacking, but no satisfactory and accurate results were to be expected from the experiments in which their death point had to be determined through the intermediary of susceptible animals. Since the successful cultivation of different "spirochætes" has been effected, it has become possible to determine the effect of different chemicals. The following chart shows a summary of the results obtained in two independent series of experiments by the use of common disinfectants.

## RESISTANCE TO CHEMICALS

*At 37° C.*

Lugol kills in	1:3 dil.; 1:5-1:10 in 15 min.; 1:50 not in 1 hour.
Bichloride of mercury kills in	1:5,000 dil.; 1:10,000 in 15 min.; 1:50,000 in 30 min.; 1:100,000 not in 1 hour.

*At room temperature*

Phenol kills in	1:200; 1:1,000 in 30 min.; 1:5,000 not in 1 hour.
Lysol kills in	1:1,000; 1:5,000 not in 1 hour.
Formalin kills in	1:200; 1:500 in 15 min.; 1:1,000 not in 1 hour.
Potassium permanganate kills in	1:1,000; 1:5,000 in 15 min.; 1:10,000 not in 1 hour.

Turning our attention to the chemotherapeutic agents it is scarcely necessary to remark that, thanks to the pioneer work of Ehrlich and

his collaborators, especially to his contribution to our chemical treatment of spironematoses and trypanosomiasis, a new field of scientific research has been inaugurated. Thus Morgenroth initiated a chemotherapy for bacterial diseases by discovering various quinin derivatives as a specific for pneumococcus. Flexner and Clark, with the collaboration of Jacobs and Heidelberger,<sup>123</sup> made an extensive series of experiments in order to discover an effective chemical compound to combat poliomyelitis, wherein they obtained some encouraging results. In their early work they had employed numerous new derivatives of urotropin (hexamethylenetetramine) as this substance was known to penetrate into the intrathecal space. The work has since been extended to various bacterial infections<sup>124, 125, 126, 127</sup> as well as trypanosomiasis and spironematosis (Brown and Pearce) with the use of additional new arsenic and mercurial compounds. While I do not wish to assert that the therapeutic effect of a chemical compound has any direct relation to the latter's disinfecting or sterilizing power against the causative agent *in vitro*, it was nevertheless thought of interest to find out how these new compounds, including various derivatives of urotropin, arsenic, and mercury, would behave in relation to the various species of *Spironema* and *Treponema* in cultures.

It is a well known fact that atoxyl, arsacetin or arsenophenolglycin, and even salvarsan, attack the trypanosomes and spironemata only after being introduced into the body, where they undergo reduction and produce a highly parasitotropic component. Yet, as will be shown in the following table, salvarsan is by no means inactive *in vitro* against *T. pallidum*. It is a fairly powerful treponemicide. Hence it is not without interest to study these compounds *in vitro* and then, when completed, compare the results with their therapeutic effects *in vivo*. The test tube determination of the germicidal property of these substances should form a part of our knowledge in perfecting chemotherapy. With the cooperation of Dr. Jacobs, who is in charge of the preparation of chemotherapeutic agents at the Rockefeller Institute, the following compounds were tested on cultivated strains of *T. pallidum in vitro* with the results indicated in the tables. A fuller report will be made later by Dr. Akatsu.



TABLE II

No.	Preparation	Concentration sufficient to kill T. pallidum	Concentration which no longer kills T. pallidum
9.	<i>p</i> -Bromobenzylhex. chloride .....	1:1,000	1:2,500
16.	<i>o</i> -Xylylenedi-hex. chloride .....	1:2,500	1:1,500
19.	2-Nitro-3, 4-Dimethoxybenzylhex. chloride .....	1:2,500	1:1,500
21.	1-( <i>ω</i> -chlorobenzyl)-2-oxy-3-naphthoic methyl ester) + hex. ....	1:2,500	1:1,500
28.	5-Chloromethylvanillin+hex. ....	1:750	1:1,000
29.	5-Chloromethylsalicylic acid+hex. ....	1:2,500	1:1,500
40.	<i>p</i> -iodobenzylbromide+hex. ....	1:750	1:1,000
46.	<i>o</i> -nitrobenzylchloride+hex. ....	1:250	1:500
47.	<i>p</i> -nitrobenzylhex. chloride .....	1:750	1:1,000
50.	Methylhex. iodide .....	1:100	1:250
84.	Chloroacetamide+hex. ....	1:1,000	1:2,500
86.	Oxymethylchloroacetamide+hex. ....	1:250	1:500
90a.	Ethyl bromoacetate+hex. ....	1:1,000	1:2,500
96.	Chloroacetylaniline+hex. ....	1:1,000	1:2,500
97.	$\beta$ -acetoxy- $\alpha$ -chloroacetyl naphthobenzylamine+hex. ....	1:1,000	1:2,500
102.	Chloroacetyl- $\alpha$ -naphthylamine+hex. ....	1:500	1:750
107.	Chloroacetylbenzylamine+hex. ....	1:500	1:750
109.	Chloroacetyl- $\beta$ -naphthylamine+hex. ....	1:1,000	1:2,500
111.	<i>o</i> -Methylchloroacetylbenzylamine+hex. ....	1:2,500	1:5,000
112.	Chloroacetyl- <i>p</i> -aminobenzoic ethyl ester+hex....	1:1,000	1:2,500
114.	Chloroacetylurea+hex. ....	1:1,000	1:2,500
121.	Phenoxyethylhex. bromide .....	1:250	1:500
122.	<i>p</i> -Bromo chloroacetylaniline+hex. ....	1:2,500	1:5,000
126.	Chloroacetylaminooztoluene+hex. ....	1:250	1:500
134.	Chloroacetyl- <i>p</i> -anisidine+hex. ....	1:2,500	1:5,000
138.	Chloroacetylphenylhydrazine+hex. ....	1:750	1:1,000
142.	Chloroacetoethylamide+hex. ....	1:1,000	1:2,500
146.	Menthyl bromoacetate+hex. ....	1:750	1:1,000
147.	Bromoethylphthalimide+hex. ....	1:1,000	1:2,500
148.	<i>p</i> -nitrobenzoic bromoethyl ester+hex. ....	1:250	1:500
150.	Bromoethyl benzoate+hex. ....	1:500	1:750
158.	$\beta$ -Iodopropionyl- <i>o</i> -anisidine+hex. ....	1:1,000	1:5,000
163.	<i>p</i> -ethoxyphenyl bromomethyl ketone+hex.....	1:500	1:750
164.	Chloroacetyl- $\psi$ -cumidine+hex. ....	1:2,500	1:5,000
168.	<i>p</i> -Acetamino- $\omega$ -bromoacetophenone+hex. ....	1:750	1:1,000
171.	<i>m</i> -Chloroacetylaminomethylbenzamide+hex. ....	1:1,000	1:2,500
172.	<i>m</i> -Chloroacetyl- $\alpha$ , $\alpha$ ,-phenylbenzylhydrazine+hex..	1:2,500	1:5,000
174.	Chloroacetyl-aminoethyl anisate+hex. ....	1:500	1:750
204.	3-( $\omega$ Bromoacetyl) quinaldine+hex. ....	1:2,500	1:5,000
218.	Tribromo- <i>p</i> -eresyl bromoethyl ether+hex.....	1:2,500	1:5,000
219.	Chloroacetyl- <i>p</i> -aminoleucomolachite green+hex.*.	1:5,000	1:7,500
229.	Chloroacetyl- <i>p</i> -aminobenzeneazo- <i>p</i> '-dimethylaniline +hex.* .....	1:500	1:750
232.	<i>p</i> -Chloroacetylaminobenzeneazo- <i>p</i> '-diethylaniline+ hex. ....	1:1,000	1:2,500
234.	$\alpha$ -naphthyl bromoethyl ether+hex.....	1:500	1:750
239.	<i>o</i> -Acetaminophenyl bromoethyl ether+hex.....	1:1,000	1:2,500
242.	<i>p</i> -chloroacetylaminodiethylaniline+hex. ....	1:1,000	1:2,500
244.	Hex.+chloroacetylaminooethyl <i>p</i> -nitrobenzoate....	1:2,500	1:5,000

TABLE II—(CONT'D)

No.	Preparation	Concentration sufficient to kill <i>T. pallidum</i>	Concentration which no longer kills <i>T. pallidum</i>
249.	Chloroacetyl- <i>p</i> -aminodipropylaniline+hex.* .....	1:500	1:750
252.	Chloroacetyl- <i>p</i> -aminotetraethyl- <i>p'</i> , <i>p''</i> -diaminotriphenylmethane+hex. ....	1:1,000	1:2,500
253.	Chloroacetyl-diethylamine+hex. ....	1:1,000	1:2,500
255.	<i>p</i> -Cyanobenzylhex. chloride. ....	1:1,000	1:2,500
257.	Chloroacetyl- <i>o</i> -aminophenyl benzoate+hex. ....	1:1,000	1:2,500
261.	Chloroacetyl-triphenylmethylamine+hex. ....	1:1,000	1:2,500
262.	Chloroacetyl-leucosauramine+hex. (*?) .....	1:1,000	1:2,500
263.	Chloroacetyl-aminoethyl <i>o</i> -nitrobenzoate+hex. ....	1:1,000	1:2,500
267.	Chloroacetyl-aminoethyl $\beta$ -naphthoate+hex. ....	1:2,500	1:5,000
271.	Chloroacetyl- <i>N</i> -phenylaminoethyl- <i>p</i> -nitrobenzoate+hex. ....	1:1,000	1:2,500
272.	<i>m</i> -Acetamino- <i>p</i> -tolyl $\omega$ -iodoethyl ketone+hex. ....	1:5,000	1:7,500
273.	Chloroacetyl-ethylaminoethyl <i>p</i> -nitrobenzoate+hex. ....	1:1,000	1:2,500
278.	$\alpha$ , $\beta$ -Diphenylchloroacetyl-amino-ethanol+hex. ....	1:250	1:500
280.	Chloroacetyl- <i>m</i> -aminoacetophenone+hex. ....	1:1,000	1:2,500
282.	$\alpha$ -Phenyl- $\alpha$ -oxy- $\beta$ -chloroacetyl-aminoethane+hex. .	1:1,000	1:2,500
283.	<i>p</i> -nitrobenzoylaminoisopropyl chloroacetate+hex. .	1:500	1:750
288.	Iodopropanol+hex. ....	1:500	1:750
289.	2-Chloroacetyl-amino-3-oxy-3-methylbutane+hex. ..	1:2,500	1:5,000
291.	Chloroacetyl- <i>o</i> -methylphenoxyethylamine+hex. ..	1:1,000	1:2,500
293.	Chloroacetyl- $\beta$ -amino- $\delta$ -butanol+hex. ....	1:250	1:500
298.	$\beta$ -Phenyl- $\beta$ -oxy- $\delta$ -chloroacetylaminopropane+hex. .	1:1,000	1:2,500
301.	$\beta$ -Naphthyl bromomethyl ether+hex. ....	1:1,000	1:2,500
303.	2-oxy-3, 5-dibromobenzyl bromide (+?) +hex. ....	1:1,000	1:2,500†
308.	Chloroacetyl- <i>m</i> -iodoaniline+hex. ....	1:750	1:1,000
309.	Chloroacetyl-5-iodo- <i>o</i> -toluidine+hex. ....	1:750	1:1,000
M1.	(4[p-oxybenzeneazo]-phenylmercuric acetate) ....	1:50,000	1:75,000
M4.	[oxybenzylideneamino] phenylmercuric acetate+ .....	1:50,000	1:75,000
M7.	1-Amino-2-[ <i>p</i> -naphthaleneazophenylmercuric acetate]-5-sulfonic acid .....	1:25,000	1:50,000

Hex.=Hexamethylenetetramine.

\* = Grind up in a mortar with a little water and add N/10 HCl carefully until dissolved.

† = Treat as above, using N/10 NaOH instead of HCl.

Table II gives a general survey of these compounds, while Table III puts down the strengths of various well known disinfectants and chemicals for the sake of comparison. Table IV gives the resistance of several culture strains of pallidum and other allied species to the action of two different new compounds.

As briefly mentioned the spiro-nemicidal (or treponemicidal) power of salvarsan and neosalvarsan is alleged to increase considerably when introduced into the living body. In a series of experiments,<sup>122</sup> it was found that by allowing a sterile extract of freshly removed rabbit's

TABLE III

Names of substances	Concentration sufficient to kill <i>T. pallidum</i>	Concentration in which <i>T. pallidum</i> survived
Phenol .....	1:2,500	1:5,000
Formalin .....	1:750	1:1,000
Lysol .....	1:5,000	1:7,500
Sublimate .....	1:100,000	1:500,000
Salvarsan .....	1:7,500	1:10,000
Neosalvarsan .....	1:2,500	1:5,000
Atoxyl .....		
Sodium iodide .....	1:10	1:25
Potassium iodide .....	1:10	1:25
Lugol's solution .....	1:75	1:100
Iodox. benz. acid.....	1:500	1:1,000
Trypозofrol .....	1:25,000	1:50,000
Neetpозofrol .....	1:250	1:1,000
Sodium cholate .....	1:5,000	1:7,500
Sodium glycocholate .....	1:2,500	1:5,000
Sodium taurocholate .....	1:2,500	1:5,000
Sodium oleinicum .....	1:70,000	1:50,000
Saponin .....	1:75,000	1:100,000
Cholesterin .....	No action	No action
Cobra lecithid .....	1:1,000	1:5,000
Cobra venom .....	1:1,000	1:5,000

TABLE IV

Names of organisms	Preparation M1			Preparation No. 253	
	1	1	1	1	1
	10,000	25,000	50,000	1,000	2,500
<i>T. pallidum</i> , heavy type.	..	—	+	—	+
<i>T. pallidum</i> , thin type.	—	+	..	—	+
<i>T. calligyrum</i> .....	..	—	+	—	+
<i>T. mucosum</i> .....	..	—	+	—	+
<i>T. microdentium</i> .....	..	—	+	—	+
<i>S. refringens</i> .....	..	—	+	—	+

liver or defibrinated blood of the same animal to act upon neosalvarsan for three hours at 37°C. the germicidal power of this drug increased from 1:1,000 to 1:2,000 in the case of the liver extract, and from 1:1,000 to 1:5,000 in the case of the blood. The addition of boiled extract had no such activating effect.

*Acquisition of Increased Resistance to Drugs.*—It will be recalled here that the failure of chemotherapy in trypanosomiasis in man

and animal is partly due to the production of so-called drug-fast strains of various trypanosomes after the latter have on several occasions been subjected to the action of certain arsenic compounds. These organisms will be destroyed to a great extent by the first injection of the drugs, but if there remain a few which have resisted the first medication, they will multiply and the animal will once more be infested with the organisms. The offspring is more resistant to the action of the same drug than the preceding generation. A large dose of the medicament is necessary to destroy the organisms and to overcome this increased resistance. But as a matter of fact, the increased resistance of the organism to the drug is relatively much greater than that of the infected hosts and the limit will soon be reached beyond which the quantity of the drug cannot be further increased without seriously affecting the infected man or animal.

Experiments of this nature have been made with atoxyl, arsacetin, arsenophenylglycin, etc. To employ Ehrlich's terms, the organotropic affinities of these drugs were so close to the parasitotropic, that it was impossible to employ a sufficient quantity to completely sterilize the infected body, since the administration of such a quantity would mean death or the serious impairment of some of the functions. Ehrlich's conception of a specific chemotherapy was based upon the fact that different cell groups are provided with their characteristic receptor apparatus (chemoceptor), to which a given chemical molecule attaches by means of its side chains. Thus, for trypanosomes there are certain receptors which will fit in with a certain atom complex of atoxyl, arsacetin, etc., while of the infected hosts the organs show much less affinity for them. In developing chemotherapy for syphilis, Ehrlich finally evolved a compound in which the spironematropic atom complexes were far more in excess than the organotropic groups. This compound, as is universally known, is dioxydiamidoarsenobenzol, better known as salvarsan. According to Hata<sup>126</sup> the ratio of the dosis curativa and dosis tolerata of this compound is 1:3 for mice and rats infected with *Spiroplasma recurrentis*, and 1:58 for chickens with *S. gallinarum*, while in the case of experimental chancre in rabbits it is between 1:7-1:10. In these animals Ehrlich's *Therapia sterilisans magna* was achieved as also in cases of relapsing fevers in man. In human syphilis, however, in spite of the most powerful spironemicidal action, his original

aim to sterilize the syphilitic body with a single injection of a large dose was not uniformly attained.

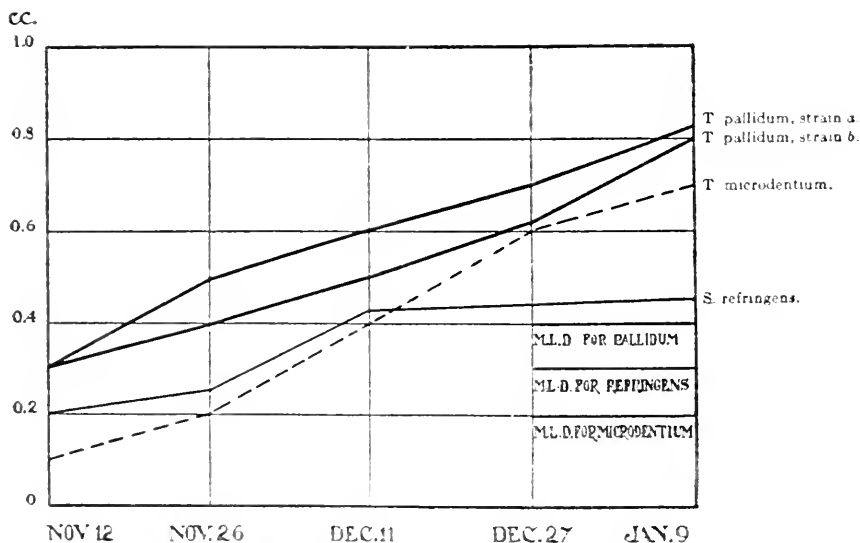
Yet there is no doubt that a prompt administration of salvarsan in a sufficient dose during the early stage of infection sterilized the patients, as was evidenced by the increased instances of permanent abortion of the infection and of reinfection after the salvarsan treatment. On the other hand, we are also confronted with repeated recidives in certain patients. We often hear of mercury-resistant as well as salvarsan-refractory cases. It has been known for some time that *Spirosonema recurrentis* as well as *Spirosonema duttoni* produces an arsenic-fast strain in mice or rats when the latter are treated with atoxyl, arsacetin, etc. In this respect these spirosonemata resemble trypanosomes. Marks<sup>129</sup> once considerably raised the resistance of a bacteria to arsenious acid by allowing it to gradually accustom itself to the action of this chemical in test tube cultures. It, therefore, seems not at all improbable that *Spirosonema* as well as *Treponema* become more resistant to the parasitotropic effect of arsenic compounds and possibly of mercurial salts, not only *in vivo*, but *in vitro*. Akatsu carried out a number of experiments in my laboratory in which he has apparently succeeded in raising to many times their original degree the resistance of the *Treponema* group to salvarsan, neosalvarsan, and bichloride of mercury. The experiments were carried out with cultures of these organisms, the general plan being to cultivate the organisms in media containing these substances in a concentration just short of that required to suppress the growth completely, and to make subcultures from it into new media containing somewhat greater quantities of the chemicals than the preceding series. In the present experiments fluid cultures consisting of ascitic fluid and a piece of fresh rabbit's kidney covered with a layer of liquid paraffin were employed. Subcultures from one medicated culture to another were made at two weeks' intervals, during which time the general condition of the cultures could be estimated. As mentioned above, subcultures are made from tubes still showing numerous actively motile organisms. It is difficult to carry on the culture if one attempts to make a subculture in which too much medicament is present to give a fairly good growth, since no growth will be obtained in a subculture which has been inoculated

with a poor culture arrested in its development by an excess of the drugs.

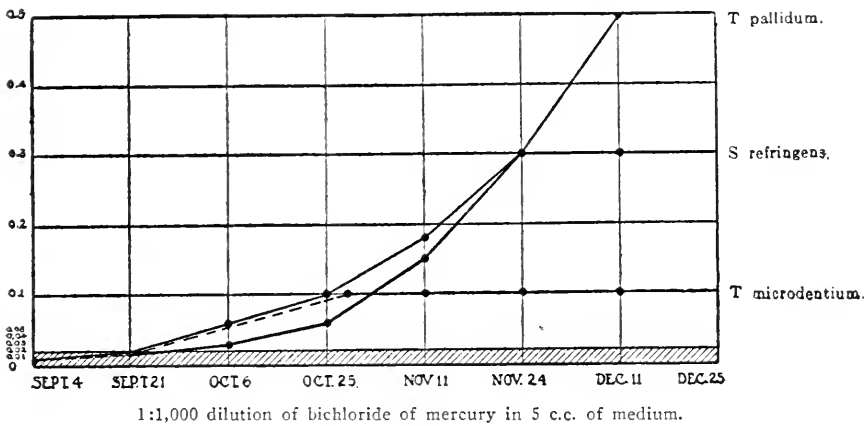
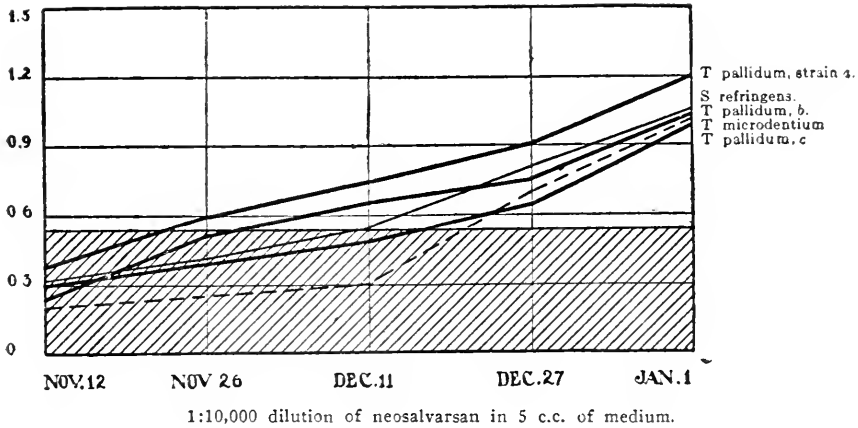
In order to suppress the growth of various treponemata which had not previously been in contact with these compounds, the following doses were found necessary in a total volume of 5 c.c. of the culture medium. The solutions of salvarsan and neosalvarsan were 1:10,000 dilution in water, and bichloride of mercury 1:1,000 dilution. Salvarsan was neutralized with NaOH, as usual.

	SALVARSAN	NEOSALVARSAN	HgCl <sub>2</sub>
Refringens	0.4 c.c.	0.6 c.c.	0.02 c.c.
Pallidum (two strains)	0.375 c.c.	0.5 c.c.	0.02 c.c.
Microdentium	0.2 c.c.	0.3 c.c.	0.02 c.c.

It will be seen from the charts that the resistance of different species of *Treponema* and also of different strains of the same species (*T. pallidum*) seemed to increase gradually until at the end of ten weeks (five transfers), they were still able to grow very well in a medium which contained several (2 to 3.5) times the quantity of the arsenic compounds originally sufficient to restrain their growth completely. In case of bichloride of mercury the increased rate of tolerance was still more striking within a certain limit of concentra-



1:10,000 dilution of salvarsan in 5 c.c. of medium.



tion, but there was no further increase in resistance when the medium contained more than 0.5 c.c. of the 1:1,000 dilution of this salt. The tissues which usually remain fleshy pink in color for several days became quickly discolored and a dirty grayish black when mixed with the above concentration of  $\text{HgCl}_2$ .

The question of the duration of the acquired resistance to the drugs has not yet been studied a sufficiently long time to draw any conclusions, but the resistance has remained unmodified for at least three generations. It may be mentioned that *Spironema recurrentis* was carried through two generations in mice without undergoing any change in its acquired drug-fastness.

## TRANSMISSION OF SPIRONEMA AND TREPONEMA TO MAN AND ANIMALS

Under natural conditions the transmission of a blood-inhabiting *Spirochaeta* to man or animals is effected through the bite of an infected blood-sucking insect. The transmitter in each instance is highly, if not strictly, specific, although other blood-sucking insects may also be infected by sucking the blood of an animal which is suffering from an infection with any of the pathogenic blood spirochetes. These unnaturally infected ticks, bedbugs, fleas, or lice are not good transmitting agents as compared with the natural carrier of the infection. That the *Spirochaeta* in such nonspecific insects can survive for some time can be shown when the disease is produced in a susceptible animal by inoculating it with the crushed material of the infected insects. It is possible, therefore, that an infection can be occasioned by smearing the excreta or crushed body contents of the infected insect over any defect of the epidermic layer of a susceptible subject. For example, in the case of *Spirochaeta recurrentis*, both body lice and bedbugs may be infected by sucking the blood of a patient suffering from the European relapsing fever, but the lice alone can transmit the disease to the next person they bite. Bedbugs are never known to spread the infection by their bites although by crushing the infected bugs directly over a minute skin trauma (scratch, etc.), a person may become infected. A brief summary is given below of the natural intermediary hosts of different bearing spirochetes, as well as certain experimental data bearing on the role of other blood-sucking insects and on the susceptibility of various animals of each *Spirochaeta*.

*Spirochaeta recurrentis*, the causative agent of the European relapsing fever, is naturally transmitted by *Pediculus corporis*. *Pediculus capiti* was found by Gonder to be incapable of transmitting the disease, although its body may contain the organisms. The common bedbugs (*Cimex lectularius*) may likewise harbor the *Spirochaeta* for as long<sup>120, 121, 122</sup> as sixty days, but according to the experiments of various investigators, does not spread the infection. The rat louse (*Hematomys spirulosis*) can carry the infection from rat to rat, while the monkey louse does the same among monkeys. Breinl and Kinghorn,<sup>123</sup> as well as Neumann,<sup>124</sup> Manteufel,<sup>125</sup> and Sargent and Foley<sup>126</sup> succeeded in transmitting the infection to rats with ticks (*Ornithodoros moubata*). Schuberg and Kuhn report a successful transmission by *Stomoxys*, the blood-sucking flies.



The infection can be transmitted subcutaneously as well as *per os* in experimental animals.

Infected organs fed to rats produce the infection in these animals, as shown by Uhlenhuth and Haendel,<sup>137</sup> and others. Manteufel considers the uninjured skin permeable to *S. recurrenti*, and Nattan-Larrier produced the infection *per vagina*, *per penis*, etc., in rats, while Gozony successfully transmitted the disease also by means of subcutaneous, conjunctival, and intestinal application of the *Spiro-nema*. Schellack,<sup>138</sup> who obtained a positive result in one out of twenty-eight experiments on rats, was able to demonstrate a microscopical defect of the skin at the point of entrance. The organism is experimentally transmissible to monkeys, and from monkeys to rats, mice, guinea pigs, and sometimes rabbits.

*S. duttoni*, the causative agent of the African tick fever, is normally carried by *Ornithodoros moubata*, as was recognized by Dutton and Todd,<sup>139</sup> and Koch.<sup>139</sup> The last named investigator discovered the *Spiro-nema* in the ovaries four to five days after the tick had sucked the infected blood. Carter<sup>140</sup> confirmed this finding, while Neumann<sup>134</sup> found the organisms in freshly laid eggs. Hereditary infection for one or more generations was shown to occur by the study of Dutton and Todd, Wolbach,<sup>141</sup> and others. The tick is infectious an hour after sucking and remains so as long as 90 days (Wittrock<sup>142</sup>). This author always found the *Spiro-nema* in the infective ticks. *Ornithodoros savignyi* has been suspected of carrying the infection,<sup>143</sup> and Brumpt once succeeded in infecting a monkey by this tick. Robledo holds *Argas americanus* responsible for the spreading of *S. novyi* (the American type of relapsing fever) in Columbia, but this theory calls for further investigation. According to Breinl and Kinghorn,<sup>144</sup> the rat's fetus may be infected through the placenta when a mother rat is inoculated with *S. duttoni*. The organism is experimentally transmissible to rats, mice, monkeys, guinea pigs, and rarely to rabbits.

As has been briefly mentioned elsewhere, Leishman, Fantham, Hindle, and others assume a granular or coccoid phase in the life history of this and allied species, and maintain that the *Spiro-nema* gradually undergoes granulation when it reaches the tick's body and multiplies in the Malpighian tubules and ovaries. The tick becomes infective after an incubation of 1 to 2 days at 37°C. Hindle<sup>70</sup>

demonstrated the infectivity of the coxal fluid in which he found numerous granules and some spironemata. This investigator thinks that the Spironema or infective granules in the coxal fluid enter the body of persons through the wound produced by the bite of the tick. The infected eggs become infective after being incubated, as was demonstrated by Hindle by injecting the crushed material into the susceptible animals; Leishman<sup>145, 146</sup> found numerous spiral rods in the infected tick eggs when the latter were incubated for a few days at 35°C. Schubert and Manteufel showed the infectivity of the ticks to be lost when they are kept at a temperature below 22°C., but Gonder failed to find any such difference. Marchoux and Couvy, Gleitmann, Wolbach, Wittrock, Kleine and Eckard, and others, believe that, wherever infectivity is present, there are always to be found some typical spironemata, either in the tick or in its eggs.

*Spironema berbera* (the North African type) is carried by *Pediculus corporis*, but not by *Argas*, the flea or bedbug<sup>147, 148</sup> (Sergeant, Gillet, and Foley). *S. carteri* is also transmitted by body lice. In this case Mackie<sup>149</sup> found the organisms more numerous in the female lice than in the male; they are distributed in the mouth, stomach, and digestive tract. Mackie believes, however, that *Acanthia lectularia* sometimes carries the infection.

Among the ticks which transmit Spironema in cattle and sheep may be mentioned *Boophilus decoloratus* and *Rhipicephalus evertsi*. The virus is carried by heredity. The causative agent of chicken fever, *S. gallinarum*, is carried by *Argas persicus* under natural conditions, while other species (*Argas reflexus* and *Argas miniatus*) can transmit the disease experimentally.<sup>138</sup> *Ornithodoros moubata* is doubtful, as Schellack<sup>136</sup> failed to produce the infection while Fülleborn and Mayer<sup>150</sup> claim a success with this organism. Schellack was able to produce the infection in 3 out of the 15 experiments performed by him on chickens by the percutaneous application of the infected blood. Feeding fowls with infected ticks may cause the infection. The organism is experimentally transmissible to ducks, geese, sparrows, canaries, and sometimes rabbits. *S. ictero-hemorrhagia*, the causative organism of Weil's disease, has been shown by Inada and his associates to be but rarely conveyed by direct contact, but no natural intermediary hosts have been discovered. The organisms are abundantly present in the urine during the

convalescent stage and they are fully virulent for guinea pigs. According to the experiments of Inada and his associates, the *Spiro-nema* as contained in the liver emulsion is capable of penetrating an apparently uninjured skin of the guinea pig a short time after contact (5 minutes is sufficient to cause infection).<sup>\*</sup> Therefore, it is altogether possible to infect a person through direct contact with some of the excreta of a patient. The infection can be induced in guinea pigs by introducing the infected material into the stomach after it has been previously neutralized with bicarbonate of soda. In regard to the *Spiro-nema* found by Futaki and others at the site of or in glands adjacent to the rat bite, we must assume that this represents the occurrence in rats of a pathogenic *Spiro-nema* which produces fever and other symptoms when transmitted to human subjects. Further investigation in this direction is most desirable. The organism is most easily experimentally transmissible to guinea pigs. Monkeys, rats, and mice are less susceptible.

Prior to Futaki's work there appeared a report by Kitagawa and Mukoyama, who also found a *spiro-nema* in the inflamed tissue of the bitten finger of a woman. By transmitting the tissue into guinea pigs and white rats, these authors claim to have reproduced symptoms resembling the so-called rat-bite fever. In the smears of the kidney and liver taken from the dead animals, they found two types of spiral organisms; namely, in the guinea pig tissues, the refringens type; and in the white rat, the minute and short type. In examining the preparations kindly sent to me by the authors, I found their findings to be entirely correct, but the refringens type is more like *T. microdentium* and a large number of bacteria, such as fusiform bacilli, and big rods, etc., were also present in the same preparations. As to the short type, one can only say that its morphology is almost indistinguishable from that of *S. muris* or *S. microgyratum*. These organisms do not agree with the illustrations and description of the *Spiro-nema* reported some time later by Futaki and others. In the case of Kitagawa and Mukoyama, the local and general symptoms may have been due to a mixed infection by the oral flora of a rat.

The *Spiro-nema* of relapsing and tick fevers also cause in man a well characterized type of fever accompanied by two attacks inter-

<sup>\*</sup>Of eight guinea pigs experimented upon, only one escaped the infection which developed in from ten to twelve days with typical symptoms.

rupted by a period of apyrexia lasting several days. During the apyrexia the blood is free of the parasites. But it is not at all rare for the recidive to be repeated more than once. While at the highest point of the fever the organisms are most abundant in the blood, they are also present in different organs. Dutton and Todd, Breinl, Leishman, and Fantham believe that the spironemata are taken up by phagocytes within which they undergo transformation into the granular phase which in turn gives rise to the new generation of spironema. Balfour considered the intraglobular forms of *Spironema granulosa penetrans* (similar to, probably identical with *S. gallinarum*) as asexual, and the extracellular forms as a sexual phase. Fantham observed some extracellular granules which may start the relapse. Darling would hold the phagocytized spironemata within the endothelial cells of the liver responsible for the source of the recidive, as he found the organism to remain intact for some time during convalescence. Grabitschewsky sees in the surviving resistant specimens, which had been shielded from destruction in various organs, the progeny of the organisms producing the second attack. In the case of *S. carteri*, Mackie assumed the possible existence of an ultramicroscopic phase, as the serum taken from a patient at the apyrexia period is said to be infective in spite of the absence of any spiral forms. It may be remarked that to detect a sparse number of any Spironemata under the microscope is one of the most difficult tasks, and one is very liable to overlook the organism.

*T. pallidum* and *T. pertenue* are the only pathogenic varieties among the group. In the case of syphilis our knowledge is quite complete, so far as the mode of transmission is concerned. On the other hand, much still remains to be learned regarding the manner in which yaws is communicated from person to person. Probably, like syphilis, its infection is spread by direct contact with a patient or any object which, after having been in contact with a patient, harbors the live organisms, although the possibility of transmission through flies, mosquitoes and ticks is not excluded. Castellani and Chalmers<sup>151</sup> quote an instance in which a fly which sucked on a yaws papule infected a monkey whose eyebrow was scarified. Modder<sup>152</sup> assumes transmission of yaws by ticks (*Argas* and *Ixodes*) in Ceylon. It is said that vaccination and wet nursing spread the infection.

In order to facilitate their entrance into the human body both organisms need only a microscopical defect of the epidermis.

After penetrating the skin or mucous membrane, *T. pallidum* elicits a local reaction characterized by the circumscribed round cell infiltration known as chancre (primary lesion), then several weeks later, at about the time when the chancre recedes, it proceeds to enter the adjacent lymph glands and general cutaneous and mucous membrane tissues, producing roseola, papules, and flat condyloma. At this period the organisms invade almost every tissue, producing the so-called secondary symptoms. Periostitis, meningitis, iritis, and laryngitis are very frequently observed. One of the most constant symptoms is the Wassermann reaction in the blood serum.

After a period of several months longer, during which the secondary manifestations abate, another period known as the tertiary stage may supervene, accompanied by still deeper tissue destruction caused in the organisms than at any previous stages. It affects skin, bones, visceral organs, cardiovascular system, and central nervous system. The disease may be progressive or marked with alternate activity and latency. Yet in the latent period repeated abortions may occur. From the time of infection until the central nervous system is affected (general paralysis, tabes), the average period of latency of the disease is from eight to twelve years. During the tertiary stage the lesions are often gummatous and affect the connective tissue muscles and blood vessels, while in cases of general paralysis and tabes the parasites diffusely pervade the parenchyma,<sup>153, 154, 155, 156.</sup> This form is a syphilitic parenchymatous encephalomyelitis. In acquired syphilis *T. pallidum* has been demonstrated in every syphilitic condition. It was first demonstrated in the primary and secondary lesions by its discoverers, Schaudinn and Hoffmann; in liver gumma, by Schaudinn; in aortitis, by Wright and Richardson,<sup>157</sup> Schmorl,<sup>158</sup> and Reuter;<sup>159</sup> in arteritis cerebialis, by Bender;<sup>160</sup> in heart muscles and pancreatitis, by Warthin;<sup>161</sup> in adrenal glands, by Hoffmann,<sup>162</sup> Jacquet and Sézary;<sup>163</sup> in nephritis, by Hoffmann,<sup>164</sup> in the cerebrospinal fluid, by Hoffmann,<sup>165</sup> Niehols and Hough,<sup>166</sup> and Sézary and Paillard;<sup>167</sup> in the blood during the secondary stage, by Uhlenhuth and Mulzer;<sup>168</sup> in paresis, by Graves;<sup>169</sup> in interstitial keratitis, by Igersheimer;<sup>170</sup> in cerebral gumma, by Dunlap;<sup>171</sup> in the paretic brains, by Noguchi and Moore,<sup>172</sup> Mari-

nesco and Minae,<sup>173</sup> Levaditi, Marie and Bankowsky,<sup>174</sup> Mott, Rosenoff,<sup>175</sup> Tomaszewski and Forster,<sup>176</sup> Wile,<sup>177</sup> and others; in spinal cord, by Noguchi,<sup>178</sup> Versé,<sup>179</sup> and others. It should be mentioned that the first demonstration of *T. pallidum* in sections of tissues from acquired syphilis was accomplished by Bertarelli and Volpino,<sup>180</sup> by means of their silver impregnation method which has since been superseded by a similar procedure amended by Levaditi.

In congenital syphilis the number of organisms present in the different organs and in different fetuses varies greatly. In some it may be extremely tedious to demonstrate the organisms, in others the whole fetus may be thickly interwoven with the intertwining nets of treponemata. The favorite site of invasion is the liver and skin, although stomach, intestines, adrenals, kidney, spleen, heart muscles, pancreas, bone marrow, lymph glands, thymus, testes, ovaries, and brain have been shown to contain the parasites, even in large numbers in certain instances.<sup>181</sup> The placenta and navel cord are also affected. For the first demonstration of the organisms in congenital lues, we are indebted to Levaditi,<sup>182</sup> who introduced his well known silver impregnation method for this study. According to personal experiences in connection with syphilitic infants who lived several days after birth, the number of pallida present was always very small and it sometimes required many hours' search to find a single specimen. A striking difference between syphilis and yaws is the absence in yaws of visceral affections and of the nervous involvement. Much yet remains to be investigated with regard to the relationship between syphilis and yaws, the causative agents of which bear so great a morphological, and, to a certain extent, a biological resemblance toward each other.

The transmissibility of syphilis to animals was long the subject of study by earlier investigators, but the first conclusive experiments in this connection were furnished by Metchnikoff and Roux<sup>183</sup> who succeeded before the discovery of *T. pallidum* by Schaudinn in producing the primary and secondary lesions in the chimpanzee. It was also shown that these lesions were transferable to further series of animals. Immediately after the discovery of *T. pallidum* in human syphilitic tissues, Metchnikoff and Roux found the same organism in experimental syphilis, thus closing up the first link of the chain of evidence which was to prove the specificity of the organism for syphilis. They also infected macacus monkeys with the virus derived from the chim-

panzee. Soon afterward Schultze<sup>184</sup> and Bertarelli<sup>185</sup> produced syphilitic keratitis in rabbits, while Parodi<sup>186</sup> selected the testes (intratesticular) to transmit the human strain to the rabbit. This work has been extended and elaborated by later investigators, particularly by Neisser,<sup>187</sup> Hoffmann, Loehe, and Mulzer,<sup>188</sup> Uhlenhuth and Mulzer,<sup>189</sup> Grouven,<sup>190, 191, 192</sup> Nichols,<sup>193</sup> Tomaszewski,<sup>194, 195, 196, 197</sup> and others. In monkeys the best site for inoculation is the eyebrow, while in rabbits intratesticular, scrotal, intraocular and intracardial inoculations were recommended. For the purpose of keeping up the pallidum strain, the intratesticular mode is preferable, especially when it is desired to obtain a pure material for cultivation (Uhlenhuth, Noguchi); but in case of utilizing the lesions in order to determine the effect of a therapeutic agent, Hata<sup>128</sup> recommends the scrotal chancre method introduced by Tomaszewski,<sup>194</sup> wherein he is supported by the experience of Brown and Pearce.<sup>198</sup> With the purpose of causing a generalized syphilis in the rabbit—which animal is usually refractory to the systemic pallidum infection—Grouven reports the intracardial introduction of a large quantity of the pallidum in half-grown rabbits. My own numerous attempts to produce generalized syphilis by this method completely failed, probably owing to the difference in the strains employed. It may be mentioned, however, that with a certain pallidum strains symptoms similar to human secondaries or tertiaries could be produced by means of intravenous or intratesticular inoculation. I have a few times observed iritis, keratitis, and squamous or ulcerative skin lesions, in the last of which the pallidum could be demonstrated. Nichols and Hough<sup>166</sup> were the first, however, to isolate a strain from a case of nervous recidive which constantly invaded the cornea, even before the local symptoms (testis) commenced to appear. This strain has most persistently caused keratitis and choroidoretinitis in rabbits. This phenomenon led Nichols to assume that the strain possessed a highly invasive character.<sup>199</sup> The patient from whom this strain was obtained died several months later of a rapidly progressive form of meningo-encephalitis, and the duration of the infection (from the time of the chancre to death) was very short. Nichols, therefore, considered that this case was explained by the character of the strain. Reasoner<sup>200</sup> also obtained a strain from a rapidly fatal case which was characterized by the early production of choroiditis in rabbits. In some rabbits the choroiditis was the only symptom in spite of its

being introduced into the testis or vein. While studying ten different strains of *Treponema pallidum* I was once struck with the constancy with which the various types were associated with certain distinct characters of the lesions produced in rabbits. For example, I could discern the differences among different strains in the width, length, and number of curves to a given space, etc. I divided these strains into a thick, a thin, and a medium type. The differences were great enough to enable me to identify different strains as belonging to any one of the three types.<sup>201</sup> In a series of passages covering a period of about one year and a half, it was found that the thin type produced a soft, diffusely swelling orchitis within 10 to 14 days and did not form any definite nodules even after six weeks. On the other hand, the thick type produced a hard, circumscribed nodule of varying size within about six weeks. Its development was unusually slow and the nodule remained for several more weeks. The character of the syphiloma produced by the medium type was a large, moderately firm orchitis, which started to be palpable at the end of about four weeks. As will be mentioned later, these three type strains were cultivated in an artificial medium and were found to retain their morphological characteristics unchanged. Again, my experience with the two paretic strains of *Treponema pallidum* transmitted from human brains to rabbits' testicles (using 36 rabbits for six specimens of brains) showed me that they were of lower virulence than the ordinary chancre strains in my possession, as they required 97 and 102 days respectively before the lesions could be definitely demonstrated.<sup>119</sup> With the usual skin strains four weeks' incubation is the average. Wile<sup>177</sup> recently reported a successful transmission of the pallidum from the living paretics to rabbits' testicles (using one rabbit for six specimens of brains) in which the lesions appeared within 14 days, and he concluded that the paretic strains were more virulent than the ordinary strains. It may be recalled that the persistent endeavors to produce syphilitic orchitis in rabbits by means of the paretic brains was not limited to a few investigators. Tomaszewski and Forster,<sup>202</sup> who in 1913 performed the Neisser-Pollack puncture on 62 cases at the University Institute in Berlin and found numerous examples of the motile pallida in 29 cases of the removed material, inoculated a large number of rabbits. Their results were uniformly negative. Marie, Levaditi and Bankowsky, Marinesco, Mott, and others also failed to



obtain a single positive result. Another interesting feature characteristic of the strain obtained by Wile<sup>203</sup> is the readiness with which it at once adapted itself to an artificial culture medium, generally known to be unsuitable for the purpose of obtaining an initial growth with any strain which is transmitted to the rabbits' testicle. As I have pointed out on several previous occasions, a solid medium consisting of fresh tissue, ascitic fluid and agar, is not suitable for such a purpose, and this fact has been confirmed by numerous investigators (Uhlenhuth, Zinsser and Hopkins, and others).

It will be incomplete if we pass on without reviewing the interesting observations of Graves,<sup>169</sup> who succeeded in infecting a certain number of rabbits by injecting the blood of parietic patients. Graves obtained the blood in small glass ampules (sterile) which were immediately sealed. The different specimens were put in an incubator at about 37°C., and after a number of days the contents of these ampules were inoculated into the testicles of rabbits. Although the majority of the inoculations were negative, he found a strain developing in one of the animals. Morphologically, the organisms were the typical pallidum and produced local as well as generalized reactions (ulcerative lesions near the nostrils, anus, prepuce, vagina, etc.) wherein the organisms were demonstrated. The incubation period of average duration is about three to four weeks. This strain was characterized by the early appearance of keratitis in rabbits. The observation of Graves furnishes us with a problem, viz., the fact that the sample of parietic blood sealed in a tube and left many weeks and months at an indifferent temperature was still capable of infecting a rabbit with such extreme severity. Yet Graves never succeeded in cultivating any strain of such samples; neither could he demonstrate the presence of any definite pallidum. Therefore, as Graves seems to think, *Treponema pallidum* must possess a stage of its life cycle which is still little understood by us. Can there be a resistant form which remains dormant for years until favorable conditions are secured? Clinical evidence has suggested this idea to certain syphilologists. Personal experiences with cultivated strains of *Treponema pallidum* do not justify my assuming the existence of a resistant form, except for the fact that the pallidum under cultural conditions is one of the most viable organisms. In suitable media it survives over one year when kept at

37°C., and it is not impossible that under naturally favorable conditions it may remain dormant for many years.

Several other animals besides monkeys and rabbits are susceptible of the disease. In dogs and sheep (Bertarelli, Hoffmann, Brüning), in guinea pigs and goats (Bertarelli), and in cats (Levaditi and Yamanouchi) specific keratitis has been produced. Testicles of guinea pigs (Truffi, Tomaszewski, W. H. Hoffmann, Uhlenhuth and Mulzer) and goats (Uhlenhuth and Mulzer) are also susceptible to infection by *Treponema pallidum*. Schereschewsky reported a scrotal chancre experimentally produced in a pig.

*Treponema pertenue* has been successfully transmitted into monkeys by Neisser, Baermann and Halberstädter<sup>204</sup> with skin papules, and by Castellani<sup>205</sup> with a punctate of the spleen of a patient. Nichols<sup>206</sup> transmitted it from man to *Macacus rhesus* and then from the latter to the rabbit. In the rabbit's testicle it produces a hard induration much like a syphilitic chancre. The parenchymatous orchitis finally extends over to the tunica and scrotum in which an extensive ulcerative indurated lesion results. When inoculated to the eyebrows of *Macacus rhesus*, the yaws organism produces highly destructive ulcerative papules which may remain unhealed for many months. In these lesions *Treponema pertenue* can easily be demonstrated. Halberstädter<sup>207</sup> observed a generalized eruption in an orang-outang 4 months after inoculation. In lower monkeys the lesion remains localized and heals in from three to thirteen weeks; sometimes it may result in a serpiginous recidive which tends to become diffuse.

#### FILTERABILITY OF SPIRONEMA AND TREPONEMA

According to the experiments of Novy and Knapp,<sup>13</sup> *Spirocheta recurrentis* and *S. duttoni* pass in one form or another through the pores of Berkefeld filters, the walls of which were either previously shaved off to a thickness of 1.4 to 2.5 mm. or left intact (4.2 mm.) as the filtrates obtained by this procedure were able to produce in susceptible animals a slight infection accompanied by sparse spirochetes appearing in the blood. The scarcity of the organism is ascribed to the presence of immune substances in the filtrate which was simultaneously introduced. Breinl and Kinghorn<sup>133</sup> obtained similar results with unmodified filters. In neither instance did the infective filtrates contain the Spirocheta in its spiral form. Their experiments tended

to suggest a filterable phase in the life cycle of this organism. Todd and Wolbach<sup>208</sup> report the successful filtration of the organism through the Berkefeld filters N and V, by pressures of fifty to ninety pounds to the square inch. Under these conditions the organism traversed the tortuous pores of the filters and was seen to have retained its usual spiral form when it appeared in the filtrate. Todd succeeded in finding the organisms in the filtrates of one experiment into which the control bacteria did not pass. Wolbach found the *Spironema* in the act of passing through the pores by preparing a thin section of the filter which had been employed for the filtration. He is of the opinion that the infectivity of a filtrate is due to the presence of the regular organism and not to that of filterable granules, as is assumed by others. C. Fraenkel failed to obtain an infective filtrate with any filtrates whatever.

*Spironema icterohemorrhagiæ* was found by Inada and his associates<sup>79</sup> to pass through the Berkefeld filters, grades V and N. Out of 28 experiments the filtrates were found to be infective for guinea pigs fifteen times. It is not stated whether the filtrate contained the *Spironema* in a regular form. Huebener and Reiter<sup>209</sup> also report the filterability of the virus of Weil's disease prevalent in Germany. Since they claim a spiral organism, *Spirochæta nodosa*, found by them to be the etiological agent, the same organism must be considered filterable. It passes through the Berkefeld filters V and N. As mentioned elsewhere, *Spironema nodosum* (*Spirochæta nodosa*) is probably the same organism as *Spironema icterohemorrhagiæ* (*Spirochæta icterohemorrhagiæ*) discovered a year earlier by Inada.

*Treponema pallidum* and *Treponema pertenue* are unable to pass through any bacteria-proof filters when filtered by the usual processes [application of a vacuum or a positive (compressed air) pressure]. Metchnikoff, Klingmüller and Baermann,<sup>210</sup> Casagrandi and de Luca,<sup>211</sup> and many others, established this fact in the case of syphilis, and Castellani in the case of yaws. On the other hand, the pallidum can grow through the pores of the Berkefeld filters,<sup>57</sup> grades V and N, and appear in the filtrate when provided with favorable cultural conditions for several days. On the fourth day the young forms commence to appear in the fluid which collects in the empty tube that is fitted up to receive the drops that fall by spontaneous diffusion without suction or pressure. This phenomenon, which was

first noticed and utilized by myself when obtaining a pure culture from mixed cultures, has since been confirmed by Nakano<sup>212</sup> and others.

There are yet other spiral organisms which are of great interest from the standpoint of filterability. Thus, Wolbach and Binger described *Spirochata elusa*<sup>213</sup> and *Spirochata biflexa*,<sup>214</sup> which they obtained in a filtrate of stagnant water taken from the shores of a fresh water pond in the vicinity of Boston. The first was cultivated but the second was not. With the culture of *S. elusa*, which measures about  $0.5\ \mu$  wide and  $20\ \mu$  long with an average of six to eight curves, they were able to demonstrate the organism in the filtrate within about fifteen minutes. The filtration was made by suction with the Berkefeld filters, V and N. The organism is provided with one terminal flagellum at each end and is extremely motile. *Spirochata biflexa* is a much more delicate organism. Another filterable organism, morphologically considered a "Spirochæta" in the loose sense of the term, was obtained by Wolbach and his associate, from human feces. In explaining the filterability of these rather coarse spiral organisms, which are larger than many bacteria, Wolbach considers their plasticity to be one of the important factors.

#### CULTIVATION

Only a comparatively limited number of "spirochætes" have been cultivated on artificial media. Of the free-living varieties *Spirochata plicatilis* was cultivated by Zuelzer<sup>22</sup> in a flask containing  $\frac{3}{4}$  liter of stagnant lake water and  $\frac{1}{4}$  liter of water to which a certain amount of hydrogen sulphide had been added. According to this procedure the flask is hermetically (anaerobically) sealed after the inoculation, and hydrogen sulphide occasionally introduced. The role of  $H_2S$  is to produce sulphur by oxidation, ( $H_2S + O = H_2O + S$ ). By this means the organism can be kept in culture for an indefinite period. Wolbach's *Spirochata elusa* was cultivated on a hay infusion (aerobically) where it propagates indefinitely. This organism is not allied to Ehrenberg's organism, but appears more like a Spirillum. No culture has been obtained of the molluscan cristispira. Of the Spirochæta group several varieties have been cultivated. Attempts at the cultivation of *Spirochæta novyi* by Norris, Pappenheimer, and Flournoy<sup>215</sup> were partially successful in that these

investigators were able to notice a definite multiplication of the organism in human or rat citrate blood at room temperature within 24 hours, a second generation cultivated in a similar medium bringing about the same increase the next day. A third generation was not obtained. Occasional multiplication of the *Spironema* in a defibrinated blood had previously been shown by earlier investigators (Lachmann, Albrecht, Gerhardt). Cultivation of the blood *Spiro-nema* in the strict sense of the term was achieved by the writer<sup>216, 217</sup> for the first time by employing a culture medium containing a piece of fresh tissue (rabbit's kidney, etc.), and ascitic fluid (10 to 12 cm. deep). This medium provides a condition that I proposed to designate as an *aerotropic anaerobiosis*; that is, a strictly anaerobic state is produced around the base of the fresh tissue, while the top of the ascitic fluid column has access to a certain quantity of oxygen. The whole medium may be covered with a layer of sterile paraffin oil in order to prevent evaporation of the fluid and this regulates at the same time the amount of oxygen admitted.

When the medium is inoculated with a minute quantity of the *Spironema* containing blood and then incubated at 37°C. the organism multiplies steadily until every field will show numerous motile specimens which may occur singly, in pairs, or in chains of three or more individuals. The height of multiplication is reached within four or six days, and a sudden degeneration of the organisms sets in on the seventh to the ninth day. By making subcultures on the fourth or fifth day the culture can be carried on indefinitely. It was found that the success or failure greatly depends upon the suitability of the ascitic fluid samples. A sample which forms a loose fibrin web with the fresh tissue (rabbit's kidney) within 24 hours at 37°C. gives the best empirical results. The addition of glucose or peptone seems to hinder the growth of the *Spironema*, and sterilization by filtration or fractional heating also impairs the nutrient value of the medium. Invasion of the culture by any other bacteria quickly destroys the culture; in other words, no mixed culture has been obtained. So far I have been able to cultivate *S. recurrentis*, *S. novyi*, *S. duttoni*, *S. kochi* and *S. gallinarum* by the same method. Plotz<sup>218</sup> successfully applied this method in order to obtain a culture directly from patients in Bulgaria suffering from the European relapsing

fever. According to Hata,<sup>219</sup> instead of the fresh tissue and ascitic fluid, a medium consisting of a piece of blood coagulum and serum of the horse may be satisfactorily used for cultivating *S. recurrentis*. At the temperature of 35°C. the culture in this medium remains actively motile for a month (Hata). None of the spironemata causing septicemia in man or birds have been cultivated on a solid medium, and nothing is known about such colonies. In a fluid medium they produce a diffuse opalescence, but no definite change of the medium is noticed. No odor or gas or change in the reaction has been detected in the culture. Their virulence remains unattenuated for many generations of artificial cultivation.

From the oral cavity *S. vincenti* and several spiral organisms have been obtained in pure cultures by various investigators. Tunnicliff<sup>220</sup> considers *S. vincenti* and *Bacillus fusiformis* to be identical, but different phases of development and under varying conditions. All these organisms are strictly anaerobic and can be cultivated by the usual anaerobic methods on solid media (glucose agar with or without animal proteins). They form definite colonies comparable to any other bacteria and some are putrefactive or acid-producing organisms. I am inclined to regard them as allied to *Spirillum* rather than to *Spironema*.

*Spironema icterohemorrhagiae* has been cultivated by Inada and Ito in the same medium as was originally employed by the writer for the cultivation of *S. recurrentis*, *S. duttoni*, *S. gallinarum*, etc. Ito<sup>221</sup> later succeeded in cultivating the organism on agar or gelatine containing human or guinea pig defibrinated blood in the ratio of equal parts or one to two of blood and agar or gelatine. The organism is said to grow readily on these media at a temperature of 26° to 37°C. A good growth takes place even at room temperature. Characteristic cultural features, such as gas or odor production, colonies, turbidity, etc., have not been recorded. In the fluid as well as in the solid media no visible growth was obtained. The culture is said to remain virulent for many generations and live over one month in a solid medium when kept at about 15° to 26°C.

In proportion to its clinical importance, *Treponema pallidum* has ever since its discovery in 1905 been the subject of correspondingly more numerous investigations. Volpino and Fontana<sup>222</sup> observed a temporary increase of the organisms after a piece of syphilitic tis-

sue had been put in human serum or defibrinated blood and then incubated at 37°C.; but no culture was obtained. Lebailly<sup>223</sup> claims to have kept alive the pallida in the syphilitic fetal tissue for 15 days when put in human serum at 37°C. Levaditi and McIntosh<sup>224</sup> inoculated the inactivated human serum with the expressed serum of a syphilitic lesion of a monkey containing a few pallida, and, after sealing it in a collodion sac, introduced it into the peritoneal cavity of a monkey. It was taken out after a month and was found to contain numerous motile pallida along with certain contaminating bacteria. The contents of the sac cultivated *in vivo* could be successfully transferred from one sac to another for many passages with the same result. The impure pallida cultivated by this method were avirulent for monkeys. Mühlens and Loehé<sup>225</sup> failed to confirm the above findings. In 1909 Schereschewsky<sup>226, 227</sup> claimed to have succeeded in starting an impure culture of *Treponema pallidum* by implanting a semisolidified, clear horse serum with a piece of chancre or condyloma inserted several inches below the surface. The serum commenced to liquefy around the tissue and within several days more liquefaction took place. On examining the fluid or solid medium about the tissue he found very numerous actively motile spiral organisms resembling the pallidum. Some of them were coarser and less regularly curved and looked like *S. refringens*. An enormous number of cocci or bacilli were also present. The culture gave off an intensely offensive odor. Subcultures were carried on indefinitely. The impure culture was avirulent for experimental animals. About the same time Mühlens<sup>228</sup> obtained a pure culture of an organism from a syphilitic lymphadenitis of man by first using Schereschewsky's medium and then transferring the culture to another kind of solid medium consisting of horse serum and agar. In the latter he succeeded in purifying the *Treponema* from the contaminating bacteria. Notwithstanding the fact that the organism was derived from a material in which the pallidum would be the only small *Treponema* and in spite of its great resemblance to the pallidum, Mühlens' culture has certain characteristics which, as will be seen later, render the organisms distinguishable from the pallidum cultures which were obtained by others (Noguchi,<sup>229, 230</sup> Sowade,<sup>231</sup> Tomaszewski,<sup>232</sup> Bæslack,<sup>233</sup> Zinsser, Hopkins, and Gilbert.<sup>234</sup> Thus the organisms isolated by Mühlens were avirulent, produced a strong

odor, and could grow from the beginning in a horse serum agar without the addition of any fresh tissue. W.H. Hoffmann<sup>235</sup> (1910-1911), a co-worker of Mühlens, obtained several strains which were identical with that of Mühlens, except for the fact that he was able to produce in the rabbit's testicle a somewhat acute or subacute inflammation by injecting a large quantity of solid culture.<sup>236</sup> His description of the experiments leaves the syphilitic nature of the lesion indefinitely established. The extract of the organism acted as an antigen in the Wassermann reaction, as was also shown by Schereschewsky<sup>237</sup> in the case of his impure culture; but Mühlens as well as Schereschewsky obtained similar results when extracts of other bacteria were used. Recently Zinsser and Hopkins have confirmed the nonspecific nature of so-called antigens in this type of complement fixation. Bruckner and Galasisco<sup>238</sup> (1910) and Sowade<sup>231</sup> (1911) reported the successful inoculation of rabbits by means of their impure cultures (Schereschewsky medium) given intratesticularly and intracardially. Sowade claims to have produced generalized syphilis by the intracardial injection into half grown rabbits.

During 1910-1911, I was engaged in cultivating *T. pallidum*. Unlike the previous investigators, I had chosen the testicular syphiloma of rabbits as the material for cultivation for the reason that this material affords a constant and unlimited supply of a practically pure pallidum and as many strains simultaneously as one desires to try. Besides the rabbit strains being already acclimatized to the animal, this would more readily take when a culture derived from this source is to be tested for its virulence. After unsuccessful attempts to cultivate the pallidum in all the various media, previously reported suitable for cultivation of the pallidum, and a large number of culture media and conditions having also failed, the following two methods were found to yield a positive growth of the organism on an artificial medium. As has been mentioned elsewhere, neither method is a perfect one and only a limited percentage of attempts is ever successful. The inconstant results are due partly to the different resistance offered by various strains to the artificial cultivation and partly to certain still unknown factors which enter into the composition of the media. At all events, the greatest difficulty in cultivating the pallidum is to obtain the first growth. As the number of generations increases the organism acquires an easier growth, and after a period of years of



life in the culture, the organism becomes quite saprophytic and may grow even without the addition of fresh tissues. The strict requirements demanded by anaerobiosis and by the reactions and compositions of the media become more and more lax, until the culture may adapt itself to a great many cultural conditions. The two methods above mentioned are, (1) a fluid medium consisting of a suitable sample of ascitic fluid or sheep serum water (Hiss) with the addition of a piece of freshly removed kidney or testicle from a normal rabbit; and (2) a solid medium consisting of a mixture of ascitic fluid and agar with the addition of a piece of fresh tissue as above described. The use of the fresh tissue seems to offer twofold advantages: first, as an oxygen absorbent as originally recommended by Th. Smith,<sup>239</sup> and secondly, as a source of nutrient substances needed for the pallidum. The first method (fluid medium) is applied exclusively for the cultivation of the testicular pallidum from rabbits, and the second (solid medium) is only used to cultivate the impure material derived directly from human syphilitic tissues. The first method requires an anaerobic apparatus, as a complete removal of oxygen from the atmosphere in which the cultivation is to be carried out is essential, while for the solid medium a layer of sterile, liquid paraffin poured on the top of the culture medium suffices to prevent evaporation and possibly to minimize the diffusion of oxygen into the medium. The requisite anaerobiosis is produced by the fresh tissue which lies at the bottom of the tube. I shall not enter into any technical details, but suffice it to say that nearly a dozen strains were obtained within the last few years by the use of these two methods. The strains obtained by means of the fluid medium remained for many generations unadaptable to the solid medium to which they finally grew. On the other hand, the strains grown on a solid medium could readily be made to grow when suitable conditions were provided.\* Impure pallidum cultures in a fluid medium can be purified by allowing the pallidum to grow through the pores of a Berkefeld filter. Before the associating bacteria pass, the pallidum will appear in the filtrate (by gravitation) probably on the fourth or fifth day. Some of the strains of *T. pallidum* obtained by these methods were virulent to rabbits and monkeys when tested within a few months. The lesions produced were typical in every respect,

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\*Fluid medium method.

although once the organism had entered the animal body it resisted recultivation just as much as before the first cultivation. In this respect they differ from the strains of W. H. Hoffmann,<sup>236</sup> who was able to cultivate the organisms back from the lesions into the horse serum agar without the addition of any tissue. His strains produced a strong offensive odor when recultivated. The strains cultivated in my laboratory did not and still do not give any offensive odor such as is described by Mühlens and W. H. Hoffmann. As has been stated no growth could be obtained without the aid of fresh tissue during the first year after these strains were isolated. Nor could they be induced to grow on a plain horse serum agar of Mühlens or semicoagulated horse serum of Sehereschewsky. Since attention had been called to the differences which existed between the cultures of Mühlens and Hoffmann and my own cultures, later investigators gave special attention detecting any possible production of a peculiarly offensive odor. Sowade, Tomaszewski, Bæslack, Nakano, Zinsser, Hopkins, and Gilbert failed to find any such characteristic odor in their strains. Erich Hoffmann<sup>240</sup> considers that the cultures of Mühlens and W. H. Hoffmann either contained the pallidum and a second odor-producing organism, or were not *Treponema pallidum* at all, since there exist certain pallidum-like, easily cultivated saprophytic treponemata which in pure cultures produce a strongly offensive odor (*T. microdentium*, *T. mucosum*, *vide infra*).

That the cultivated strains of *Treponema pallidum* gradually become tolerant to various media and conditions has been strikingly demonstrated by the recent investigations of Zinsser, Hopkins, and Gilbert.<sup>234</sup> Thus the investigators found that a pallidum strain which they had isolated by the original fluid culture method, described by me, gave a good growth after the tenth generation in fluid media containing different kinds of autoclaved tissues of rabbits and a mixture of slightly acid meat infusion broth with heated sheep serum. This strain likewise grows well in symbiosis with *staphylococci*, *streptococci*, *Micrococcus candidans* and *Bacillus fecalis alkaligenes* added to the sheep serum agar mixture without tissue. Addition of dead staphylococci had the same effect as symbiosis. The gelatinized horse serum or sheep serum with or without the tissue proved to be a good medium for the growth of this strain. They have obtained the same results with two other strains which were

isolated in my laboratory several years ago. The fact that during the first few years after isolation all my pallidum strains failed to grow on various media similar to those now successfully used by Zinsser, Hopkins, and Gilbert seems to indicate that rigid parasitic properties of the organism have gradually deteriorated due to the artificial cultural conditions, some undergoing the changes more abruptly than others. It is not at all improbable that in time the saprophytized strains of *Treponema pallidum* will adapt themselves to still simpler ordinary culture media. It is to be desired that efforts be directed toward improving the condition under which the organisms can be kept as nearly natural as those in living tissues, since the results obtained with completely denatured material might be quite different from those derived with the less modified material.

In summing up the pallidum cultivation one may say that the methods hitherto proposed are still imperfect and that much patience is still demanded in order to isolate a strain. Some strains remained persistently uncultivable in my hands. The strains isolated by Mühlens may have been *Treponema pallidum*; but there was no way of proving this, as his culture, which was avirulent, possessed certain properties inconsistent with those of the pallidum as subsequently defined by other investigators. The first instance, therefore, of a successful cultivation of *Treponema pallidum* was that which was carried out at the Rockefeller Institute in 1910-1911, in which were brought out not only the demonstration of the pathogenicity of the organism isolated, but also the studies of other biological characteristics of the culture.

*Treponema pertenue*<sup>241</sup> was also successfully cultivated in 1911 by the same method as that given for the cultivation of the pallidum. The material used for this work was in the form of a testicular lesion of experimental yaws in the rabbit and was supplied by Captain Nichols. The organism possessed the same cultural characteristics as the pallidum, but it was probably slightly thicker and less regularly curved. Preliminary attempts to produce lesions in rabbits ended negatively, and the strain was lost before further comparative studies could be undertaken.

Several spiral organisms were isolated from unclean lesions around the genital region. *Spironema refringens*<sup>242</sup> and *Treponema caliginum*<sup>104</sup> (from a condyloma) were cultivated by me in the pure

state by methods similar to those used for the pallidum and per-tenu. Levaditi and Stanesco<sup>243</sup> obtained impure cultures of *S. gracilis* and *S. balanitidis* by means of gelatinized horse serum. A spiral organism, *S. phagedenis*, was also obtained by me in a pure culture from a phagedenic ulcer on the genitalia of a woman, but its systematic affinity is quite uncertain.<sup>95</sup> *T. calligyrum* is slightly coarser than the pallidum, but is apt to be mistaken for the latter in cultures. It grows easily in tissue-free media.

From dental deposits of normal oral cavity *Treponema macrodentium* and *T. microdentium*<sup>192</sup> were cultivated in the pure state by means of the same methods, and *Treponema mucosum*<sup>103</sup> from the scraping of the pyorrheal gum. The microdentium and the mucosum appear very similar but can be distinguished by the production of a thin but tenacious mucin in the culture of the latter. When the culture gets old, both of these give a strong, somewhat offensive odor. This faculty to decompose the proteins (thus causing a slight turbidity in the fluid media) makes this culture readily distinguishable from the pallidum cultures, because the latter do not produce such an odor. Morphologically, they bear a great resemblance to the pallidum, although their curves are set somewhat more closely than in the pallidum. The macrodentium is more difficult to cultivate and, according to my experience, requires fresh tissue in the culture media. Morphologically, it is coarser than the pallidum and its serpentine movements and irregular, stretchable and wider curves are characteristic enough to distinguish this species from other varieties. It does not produce an odor.

Mühlens and Hartmann<sup>244</sup> succeeded in 1906 in obtaining a pure culture of *S. dentium* in the horse serum agar medium of Mühlens. In their culture they recognized a minute form of Koch's *S. dentium* type and another which approached the dimension of Hoffmann-Prowazek's *S. media* type. They suggested the possibility of these representing different stages of development or even a sexual differentiation. It appears as though their so-called pure culture may have contained more than one species. No admixture of tiny and coarse forms has been observed in the culture of the macrodentium or microdentium. The dentium culture of Mühlens produced a strong offensive odor.

## IMMUNITY AND IMMUNIZATION

The very name, relapsing fever, suggests the possibility of the development of some sort of protective power in the infected hosts against a third attack. In fact, the second attack is often milder than the first and a third relapse is rare. Persons who have had the fever are usually immune to subsequent infection for a period of several years. The same is true of the African tick fever although repeated recurrences are more frequent in this instance. Susceptible animals, such as monkeys, mice, and white rats, enjoy a period of immunity extending over about three months after recovering from the second attack. In rats no relapse has been observed. In the fowl and geese, similar immunity follows recovery from spironematosis. The studies of various investigators, especially Gabritschewsky, Pfeiffer, Novy and Knapp, Manteufel, Marchoux and Salimbeni, Levaditi and Manouélian, Prowazek, Neufeld, and others, have contributed in explaining the mechanism upon which the immunity depends. Gabritschewsky<sup>245</sup> demonstrated the presence of a specific antibody against *S. recurrentis* in the blood of convalescent patients by mixing it with the spironema-containing blood *in vitro*. The destruction of the organism occurred within a short time when the mixture was kept at a temperature of 37°C. This author considered that the development of a germicidal substance in a patient's blood was the cause of the crisis and subsequent immunity. He also recognized the appearance of a similar specific immune substance in the geese recovering from the attack of *S. anserina*. The convalescent recurrentis blood had no effect upon the organisms of goose fever and the anserina blood did not affect the organisms of the relapsing fever. The phenomena observed were agglutination, immobilization and dissolution of the organisms when mixed with their correspondingly specific bloods. Gabritschewsky produced an immune serum by injecting the horse with a spironema-containing blood. It was tested by Löwenthal in 83 cases, and in 39 cases (47%) no relapses occurred, while in 140 untreated cases, 65 had three attacks (46.5%). Novy and Knapp<sup>18</sup> confirmed and greatly extended the experimental part of Gabritschewsky's work and pointed out that the protection afforded by active as well as passive immunity is not wholly dependent upon the germicidal property, but also upon the immune bodies, since a comparatively weak germicidal blood may protect the animal against the infection in small

quantities. Besides, Novy and Knapp hold the role of the phagocytes (mononuclear, but not polynuclear) to be very important, as they ingest the dead as well as the enfeebled spirochetes under the influence of immune bodies. Levaditi and Manouélian<sup>246</sup> suggest the existence of an opsonin in this phenomenon. Mantoufel<sup>247</sup> believes the lysis of the spirochetes in the immune serum to be due to the cooperation of complement and a specific amboceptor. The rapidity and intensity with which the spirochetes are destroyed within the peritoneal cavity of actively or passively immunized rats is variable. In the peritoneal cavity of a hyperimmunized animal the organisms become granular in from two to five minutes, while in rats recently recovered from the attacks, the organisms are ingested in fifteen minutes. In passively immunized rats the spirochetes are first agglomerated and temporarily immobilized and this is followed by the appearance of some leucocytes on the scene; but the effects of the immune substances gradually wear off within about an hour. The leucocytes disappear in 30 minutes (Novy and Knapp). The germicidal and bacteriolytic actions are parallel. The duration of passive immunity in rats is less than forty days while that of the active immunity lasts nearly four months. Novy and Knapp succeeded in preparing in rats by means of hyperimmunization a powerful immune serum which contained in each cubic centimeter 500 immunity units; that is, 0.002 c.c. of the serum was able to protect the rat against 0.1 c.c. of the infective blood showing 10 to 50 spirochetes per field (2 mm. objective). In ordinary recovered rats there were only about 2 immunity units per cubic centimeter. The use of the immune blood from a hyperimmunized rat prevented the infection in the rat and cured it on its onset, but a greater amount is found necessary in order to obtain similar results in monkeys and mice as these animals are subject to a relapse after the treatment. Novy and Knapp suggested the inoculation of the Spirochete during the apyretic period in order to increase the amount of immune principles in the victim's system and thereby ward off a relapse. They found an interesting phenomenon; i. e., the injection of too much immune blood proved to be less effective than a moderate quantity. This was explained by assuming the production of a specific precipitin which acted as an anticomplement. In regard to the use of hyperimmunized blood serum in human relapsing fever, they calculated that about 375 c.c. of a serum

such as mentioned in the experimental part would be necessary and that the future of a serotherapy much depended upon the success attained in cultivating the organism in an artificial medium in large quantities. As a matter of fact we have been able to collect large quantities of comparatively pure organisms from each of the cultures of *S. recurrentis*, *S. duttoni*, *S. novyi*, *S. gallinarum*, etc., for various purposes (immunization, vaccinothrapy, etc.). In the serum of those who had just recovered from the relapsing fever, a complement fixation principle was demonstrated by Kolle and Schatilloff,<sup>245</sup> and Korsehun and Leibfried.<sup>249</sup> The reaction was said to be positive after the second attack.

In Weil's disease Inada and his coworkers found the presence of a specific spironemalysin in the serum of convalescent man or guinea pig. The immune bodies develop after the second week of the disease and may be still present in individuals who had the attack more than four years previously. The Pfeiffer phenomenon is easily demonstrated by using the organ (liver or kidney) emulsions rich in the spironemata or a culture and the immune serum in the peritoneal cavity of the guinea pig. These investigators immunized goats and horses with the cultures of the causative agent (*S. icterohemorrhagiae*) for a period of more than a year and succeeded in producing a serum which prevents the infection against the lethal dose in guinea pig in the amount of about 0.001 c.c. The clinical experience of this serotherapy which has now extended over many hundreds of cases proves to be highly encouraging.\*

The question of immunity in syphilis is rather imperfectly understood. In human subjects it was once assumed that after the first infection, complete immunity occurred as evidenced by the extreme rarity of a reinfection. Later investigators seem to consider this assumption as incorrect inasmuch as it was based upon the fact that the syphilitic individuals do not a second time contract a chancre or show a general skin eruption in spite of exposure to such an infection. This fact does not, however, necessarily denote immunity in the usual sense of the word. This state of refraction to the second infection is said to be due to the pre-existence of the same virus in the same individual who no longer reacts to the second inoculation with the original intensity or vigor, and the condition is designated by

\*Personal communication, soon to appear in print.

Neisser as "Anergie." At the same time Hutchinson showed the possibility in rare instances of an autoinoculation, while Finger and Landsteiner<sup>250, 251, 252</sup> believe that a superinfection may take place in certain syphilities. The effect of a superinfection may be a purely local manifestation or it may be subsequently followed by generalization; or it may again cause a general mobilization of the virus without a local manifestation. The character of the lesions produced by superinfection agrees with that of the lesions peculiar to different stages of the disease. If it occurs during the secondary stage, the superinfected lesion will be a papule or other exudative product, and if during the tertiary stage, the result will be a gummatous product. This alteration of various tissues of a syphilitic individual in their reactivity to the syphilitic virus is designated as "Unstimmung" by Neisser who regards this condition as a morbid state of the tissues brought about by the pressure of *Treponema pallidum*. There once prevailed a vague impression that when cutaneous tissues are extensively involved there is less likelihood of the visceral organs being invaded by the syphilitic virus and vice versa,<sup>253, 254</sup> but there is no experimental proof to support this contention. Since the introduction of salvarsan and its derivatives in the treatment of syphilis, the instances of reinfection with typical or sometimes atypical chancres are not so rare, thus indicating that after a cure has been effected the human body reacts in the usual or nearly usual manner.<sup>255</sup> This also points to the absence in such cases of any lasting immunity after the first infection has been eradicated. A thorough investigation is required in order to ascertain whether or not a certain degree of immunity develops in some of the cured cases, thereby affording protection. In some ways the question of immunity in syphilis is comparable to that in protozoan diseases, in which, though latent, no typical infection can be reinduced until the first attack is completely cured, and where no congenital immunity has yet been demonstrated.

Let me now review the situation of the immunity question in experimental syphilis. Metchnikoff and Roux, Neisser and Bruck, and others found that monkeys that have once been infected with *Treponema pallidum* may prove refractory to subsequent inoculation. Metchnikoff<sup>256</sup> thought he succeeded in protecting a monkey against the infection by inoculating it with an attenuated living virus which was no longer able itself to produce typical reactions. That the



vaccination against syphilis was not equivalent to that against variola in its fundamental principle was later demonstrated by Neisser and others, who were able to show that the monkeys that had been "vaccinated" with an attenuated virus and which were rendered "immune" to the subsequent inoculation with a fully virulent material were harboring the infection in various localities escaping the usual clinical detections. Thus the emulsion prepared from the bone marrow, spleen, etc., of the "vaccinated" animals was able to infect new susceptible animals. This phenomenon is similar to the state of anergy observed in syphilitic human subjects. Fontana,<sup>257</sup> Uhlenhuth and Weidanz,<sup>258</sup> Bertarelli,<sup>259</sup> Truffi,<sup>260,261</sup> and others, pointed out that a rabbit which carries syphilitic keratitis in one eye is not refractory or immune to the infection in the other eye. A rabbit one of whose testicles is infected with *T. pallidum*, offers no greater resistance in the other which may be infected with the virus at any stage of orchitis preceding that on the opposite side. Tomaszewski<sup>262</sup> thought that a skin infection produced in rabbits in which scrotal lesions had been persisting for about two months was much milder than in normal animals. According to personal observations, a rabbit in which a syphilitic orchitis, or keratitis, or scrotal chancre has been cured either spontaneously or through the administration of salvarsan enjoys no perceptible immunity to syphilis. Truffi repeatedly inoculated rabbits with a fetal liver emulsion containing an abundance of *T. pallidum*, but found no immunity to develop. Uhlenhuth and Mulzer immunized rabbits with the testicular pallidum emulsion without obtaining any decisive result, although in some cases they thought it exerted a beneficial influence upon the syphilitic process. In my personal experience it has been found that the susceptibility of the rabbit to syphilis is decidedly diminished in some animals by immunizing them with *T. pallidum* for several months. With a strain which gave 100 per cent takes in normal rabbits testicles, only about 60 per cent positive results were obtained in the immunized animals. This tends to show that the lower percentage of positive takes in the immunized rabbits may be due to the destructive influence of the treatment upon the invading pallida. But it was also found that in the immunized rabbits in which the inoculation succeeded, the symptoms were not any milder. In fact, not only were the local reactions just as marked as in the control

animals, but there was a tendency to the formation of generalized lesions. In two of the rabbits scrotal lesions developed after the intravenous inoculation of a virulent strain. It appears that an incomplete immunization exerts an adverse influence on the defensive factors of the rabbit. This phenomenon finds verification in the work of Grouven and Sowade,<sup>263, 264</sup> who recommended for the animal a few preliminary intravenous inoculations of the pallidum in order to insure a generalized infection through a subsequent intracardial introduction of the organisms in huge quantity. I also endeavored to ascertain whether a local administration of devitalized pallida (killed at 60°C.) on many successive occasions will not bring about a state of local immunity to *Treponema pallidum*, but my results were rather unsatisfactory, for the reason that the testicular parenchyma which was repeatedly inoculated with the pallidum emulsion underwent gradual atrophy, and the resulting hard fibrous structure was no longer a suitable test object for this fastidious parasite. Nevertheless I was able to produce small nodular lesions in two out of several rabbits so treated. Moreover, reinfection of the same tissues (cornea, testis, and skin) after a spontaneous or chemotherapeutic healing has been found possible as long as the suitable structures of the tissues are preserved.

Our knowledge pertaining to the immunity phenomena *in vitro* is of more recent date, for the test tube experiments with *T. pallidum* were made possible since the discovery of the organism and were particularly favored by the successful cultivation of the parasites on artificial media. Attempts to demonstrate the presence of a specific agglutinin for *T. pallidum* in the sera of human and experimental syphilis were made by Hoffmann and Prowazek,<sup>265</sup> Herxheimer and Löser,<sup>266</sup> Hoffmann,<sup>267</sup> Brömmum and Ellermann,<sup>268</sup> Babes and Panea,<sup>269</sup> Metchnikoff and Roux, Landsteiner and Mucha,<sup>270</sup> Zabolotny and Maslakowetz,<sup>271</sup> and others with the pallida derived from the syphilitic tissue. Their experiments were indecisive, owing to the difficulty found in obtaining a pure material free from various tissue constituents. Uhlenhuth and Mulzer<sup>189</sup> found no agglutinins to be formed in the sera of the rabbit, goat and monkey after repeated intravenous injections of the rabbit's testicular emulsion rich in the pallidum. In 1910-1911, soon after obtaining pure cultures of *T. pallidum*, we started the immunization of rabbits with different

strains of the organism. In the sera obtained from the immunized rabbits we were able to demonstrate the presence of the specific agglutinins and complement-binding principles for the cultivated pallidum strains. We were unable to produce with the sera any unmistakable agglutination of the pallidum derived directly from the syphilitic orchitis of the rabbit, but I considered this to be due to the simultaneous presence of tissue debris and other cellular elements which may have interfered with the agglutination phenomenon. These sera were not strictly specific, but contained a small quantity of agglutinins for other treponemata obtained in pure cultures. There were also a sufficient number of specific complement-binding bodies, but there was at the same time a more or less definite group reaction for other treponemata. The work was continued later by Akatsu at my laboratory with similar results. He was able to obtain a serum which could agglutinate the pallida in a dilution of 1:50,000.

In order to know whether syphilitic human sera have any definite agglutinating and complement-binding properties, a number of sera obtained from various stages of syphilis were examined with pure cultures as well as with the tissue pallidum derived from rabbit testicles. All the experiments were unsatisfactory, owing to the difficulty experienced in reading the reaction in the case of agglutination and also owing to the high anticomplementary powers of the antigens and the feebleness of the reaction in the case of the complement fixation test, except in the case of the pure culture antigens which fixed complement with the immune rabbit as well as with some of the syphilitic human sera (chiefly late and tertiary cases). According to our experiments, there is a certain degree of group reaction for the other treponemata (*T. calligyrum*, *T. microdentium*, *T. mucosum*, and *S. refringens*).

Kolmer<sup>272</sup> first described the agglutination of a pure culture of *Treponema pallidum* by the sera of rabbits injected with a living and heat-killed culture furnished by our laboratory. His results show that normal rabbit sera do not agglutinate the culture pallidum in dilutions as low as 1:20, while the sera of immunized animals produced agglutination in dilutions as high as 1:1,280. No definite agglutination was observed with human syphilitic sera in a dilution of 1:20 or higher. Nakano<sup>273</sup> also reported the presence of agglutinins in the sera of rabbits injected intravenously with a pure culture in dilutions from 1:10

to 1:70. Kissmeyer<sup>274</sup> immunized rabbits with a pure culture of *T. pallidum* and was able to obtain agglutinations in dilutions as high as 1:200,000 to 1:500,000 of the immune sera, while the sera from individuals with primary, secondary, tertiary and congenital syphilis contained agglutinins for the pallidum in dilutions of 1:100 and higher in a percentage of from 40 to 60 out of 59 cases. Normal human sera may agglutinate the pallidum in dilutions as high as 1:50. Zinsser and Hopkins<sup>275</sup> state that normal rabbit serum may agglutinate the pallidum in dilutions lower than 1:10, but the sera of their immunized rabbits (intravenous injections of the pallidum cultures) agglutinated it in dilutions as high as 1:2,000. They added that the normal as well as certain syphilitic human sera may agglutinate the culture pallidum in emulsions. Zinsser, Hopkins, and McBurney<sup>276</sup> failed to observe any agglutination when the pallida from human lesions were mixed with the immune sera (rabbits and sheep) produced with the culture pallida. Zinsser and Hopkins<sup>277</sup> demonstrated the treponemicidal bodies for *T. pallidum* (cultivated) in the immune serum produced by them.

In the sera of animals experimentally infected with syphilis the presence of specific complement-binding antibodies for *T. pallidum* has not been satisfactorily proved. It is true that we were able to demonstrate the positive complement fixation in the sera of animals immunized with cultivated treponemata, but this does not hold good when dealing with the syphilitic animal sera and the virulent pallidum strains found in tissues. On the other hand, these syphilitic sera do bind complement when mixed with pure cultures, not only of *T. pallidum*, but also of various bacteria, such as colon bacilli (Zinsser and Hopkins). Undoubtedly the phenomenon is nonspecific but pathognomonic as is the Wassermann reaction which is caused by certain lipoidal substances. These cultures must serve as the containers of the similar lipoids. Indeed, Craig and Nichols<sup>278</sup> long ago showed that the alcoholic extracts of the pure pallidum and pertenué cultures produced almost equally strong complement fixation when mixed with the human syphilitic sera, giving a positive Wassermann reaction with pure lipoidal antigens derived from other tissues. In a word, a syphilitic animal may give a positive complement fixation with various lipoids without at the same time containing any specific antibody for *T. pallidum*. In human syphilitic sera the same is also true, except in

the sera of certain late and tertiary cases in which there may be a positive reaction due to the specific antigens and antibodies in the strict sense of Bordet-Gengou's phenomenon.<sup>279</sup>

The nature of the Wassermann reaction in the sera of human and experimental syphilitic subjects is still unexplained, but one fact has been established; viz., that it is due to a peculiar change of the sera not specific for syphilis; it occurs in yaws, leprosy, trypanosomiasis, malaria (febrile period), and sometimes in malignant tumors. The fact that so many lipoidal substances as well as certain salts (sodium taurocholate, sodium cholate, etc.) derived from different sources can bring about a positive fixation precludes any strict specific antigen-antibody reaction. According to personal observations the lipotropic complement fixation reaction is not present in immune rabbit sera which have been obtained by injecting the pallida repeatedly, and which contain a large number of specific complement fixation bodies from the pallidum strains employed for their production.

Closely related to immunity is the question of allergy in syphilis. From the chronic nature of the disease many investigators considered the possibility of its occurrence at one stage or another. Jadassohn, Meirowsky, Ciuffe, Fontana, Neisser and Bruck, and others made numerous observations which rendered the presence of allergy still more probable. These investigators were handicapped by not having a pure culture of *T. pallidum*. Soon after the isolation of the pallidum strains, study of this subject was made in human syphilis with the pure material. In the meanwhile it was ascertained experimentally that the prolonged treatment of rabbits with intravenous injections of the pure pallidum culture as well as with the organisms obtained direct from the rabbit orchitis lead to the production of a state of hypersensitiveness of the skin to the inoculation of the extract of a pure, heat-killed pallidum culture.<sup>280</sup> The reaction was found to be apparently specific for *T. pallidum*. There was no injurious effect following the injection into the rabbits of the heat-killed pallidum emulsion. The emulsion, since known as luetin, was employed as a means of diagnosing human syphilitic cases, with the result that the luetin reaction was found to be most frequently present in the latent, tertiary, and congenital syphilis cases where one would naturally expect most constantly to find the allergetic or hypersensitive state of the skin. As an auxiliary or supplementary factor in producing a positive

luetin reaction, I have already pointed out that the pathological state of the skin of chronic syphilitic patients designated by Neisser as "Umstimmung" played a role in nearly 10 per cent of tertiary cases in which the skin reacted intensely to the inoculation of the control emulsion without the pallida. No efforts were made to explain this peculiarity of hypersensitiveness of the skin of certain syphilitics. But recent work of Camp<sup>281</sup> points out that the administration for many days of potassium iodide to a nonsyphilitic individual produces in the skin a hypersensitiveness to any trauma, including the inoculation of the luetin. Probably this finding may furnish the solution of the problem of Neisser's "Umstimmung," or at least of one of the contributing factors. The clinical evidence thus far accumulated seems to show, however, that in a large number of cases the luetin reaction was positive in spite of the fact that no iodide had been given during the period when the test was applied. Recently Akatsu,<sup>282</sup> at my laboratory, carried out several series of experiments regarding the influence of potassium iodide upon the reactivity of the skin of rabbits to the intradermal inoculation of the luetin, control fluid, and plain bouillon. The iodide was administered intravenously for a period of from 7 to 9 days, given in increasing doses of 0.5 to 2 c.c. of a 10 per cent aqueous solution. At the end of seven days or later the skin was tested for the luetin, control, and plain bouillon. It was found that the skin of normal rabbits did not react to the injections after the iodide treatment. There was no change in its reaction to the trauma. The skin of the rabbits which had been previously rendered hypersensitive to the luetin by means of prolonged immunization with pure pallidum cultures mostly remained the same, that is, it reacted to the luetin with the same intensity as it did before the administration of potassium iodide. Only in a few instances was the reaction somewhat intensified. There was no definite reaction to the control emulsion of plain bouillon. In some rabbits, in which the testicular orchitis after several months had shrunk to a small fibrous nodule, the luetin reaction was mildly positive, but the intensity of the reaction was but little influenced after the injection of potassium iodide, except in a few rabbits where the second tests came out more distinctly. The above findings show that the potassium iodide has no noticeable influence upon the reactivity of the skin of normal as well as syphilitic rabbits. It would be interesting to study whether in other spirocheta-

toses (relapsing fever, tick fever, rat-bite disease, and infectious jaundice) there appears any skin allergy comparable to that described for other bacterial infections (typhoid, gonorrhea, etc.). In cases of yaws, the skin reacts to the intradermal inoculations of the luetin and of the framboesin with equal intensity and cannot be differentiated by this method (Baermann and Heinemann).<sup>283</sup>

The last and probably the most important field for medicine is chemotherapy. The inauguration of modern chemotherapy by Ehrlich is as interesting as it is romantic. It can be traced back to Schaudinn's suggestive but unsupported theory that the spirochætes represent a stage of the life-cycle of trypanosomes, or at least were closely related to the latter. The introduction of organic compounds of arsenic into the treatment of trypanosomiasis was promising much when Schaudinn discovered *T. pallidum*, which he regarded as a protozoon allied to the trypanosomes. Ehrlich took up experimental chemotherapy in connection not only with the latter, but also with the newly discovered spirilloses, as he called them, including syphilis and the fowl fever caused by *S. gallinarum*. The achievement of Ehrlich and his collaborator Hata, in discovering salvarsan for the treatment of these two diseases, marks a new era in modern chemotherapy. To review this phase of the spirochæte problem would be out of the scope of my present paper. Suffice it to say that to the great pioneers, Schaudinn, Ehrlich, Metchnikoff, and Neisser, we owe an inestimable debt, not merely for their own researches, but also for re-kindling in us the sublime stimuli which have already inspired so many investigators to discover new facts, and which will continue to urge us still more to take up this task and to extend our knowledge regarding the classification, morphology, biology, pathogenesis, and experimental as well as clinical aspects of the microorganisms known as spirochætes.

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# A CONTRIBUTION TO THE ACTION OF VANADIUM WITH PARTICULAR REFERENCE TO SYPHILIS

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## WITH A CLINICAL CONTRIBUTION

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WHILE the literature on the pharmacological action of vanadium is very meager and the textbooks on pharmacology either do not mention it at all or review very briefly the fundamental work of John Priestley, much has been written on the therapeutic action of vanadium, especially by French clinicians. Neither Priestley (1876) nor Gamgee and Larmuth (1877), the first experimental investigators of vanadium, suggested a therapeutic use for it. In 1882 Witz and Osmond, two French chemists, advocated that the oxidizing properties of this element might be used to accelerate oxidations in the body. In 1899 this idea was followed by a number of French physicians, notably Laran, Lyonnet, Martz and Martin, who reported on the internal administration of vanadium in tuberculosis, chlorosis, diabetes, anemia, neurasthenia, and rheumatism, with apparently successful results. They employed the metavanadates of sodium, lithium and iron, and the so-called phosphovanadate of sodium. In 1905, Le Tanneur published his vanadiotherapy. This was merely a report on a patent medicine, Helouis' Vanadiol, and contained absurd medical theories and impossible case histories and investigations. Nothing of scientific value was presented. The only valuable work of recent date on the pharmacological action of vanadium and suggestions for its therapeutic use was published by Jackson in 1912, and will be discussed in full later.

In view of the reports of the French investigators, it is surprising that vanadium has received so little attention as a therapeutic agent. It seems that the clinical investigations reported did not impress the medical profession.

An obstacle in all the previous work has been the lack of a stable vanadium salt in solution. Heretofore, the vanadium salts used in the pharmacological investigations and in actual therapeutic use were the ortho-, meta-, and pyrovanadates of soda. In aqueous solution, these salts decompose and must be freshly prepared for medicinal use. The important prerequisite for the proper therapeutic use of vanadium is a stable neutral salt with a minimum of toxicity. There are an immense number of vanadium salts, both simple and complex, which have not, however, been investigated pharmacologically. The more stable salts are those derived from pentavalent and tetravalent vanadium. The salts of the lower oxides are too readily oxidized and many of the complex salts are either readily decomposed or are insoluble so that their use as therapeutic agents is impossible. Since elements belonging to the electro-negative subgroups of the divisions of the periodic system alone are capable of yielding alkyl derivatives, it was impossible to prepare organic derivatives with vanadium analogous to those in the arsenic series. The alkylesters of vanadium are insoluble in water, and readily decomposed and, therefore, unsuited for medicinal use. The aromatic primary amine salts of vanadium are rapidly oxidized. The salts of the nitrogen heterocyclic derivatives are insoluble and are more or less readily oxidized.

Therefore, the inorganic salts of vanadium are alone available for therapeutic purposes. In order to determine the most stable and least toxic vanadium salt, a number of simple and complex salts were prepared. These included vanadates, vanadites, and vanadyl salts, as well as the more complex derivatives with the oxides of arsenic, antimony, and phosphorus. The following salts were prepared, and their toxicity determined:

TABLE I

Colloidal Vanadium Pentoxide	$V(OH)_5$
Ammonium Metavanadate	$NH_4VO_3$
Sodium Orthovanadate	$Na_3VO_3$
Sodium Pyrovanadate	$Na_4V_2O_7$
Sodium Tetravanadate	$Na_2V_4O_{11}$
Sodium Hexavanadate	$Na_4V_6O_{18}$
Sodium Vanadite	$Na_2V_4O_9$
Aniline Vanadate	$C_6H_5NH_2V_2O_7 \cdot 2H_2O$
Vanadyl Sulphate	$VO_2SO_4$
Copper Tetravanadate	$CuV_4O_{11}$
Mercury Tetravanadate	$HgV_4O_{11}$
Ammonium Vanado-arsenate	$5(NH_4)_2O \cdot 3As_2O_5 \cdot 4V_2O_5$
Ammonium Vanadi-arsenate	$2(NH_4)_2O \cdot As_2O_5 \cdot V_2O_5$
Sodium Stibinivanadate	$14Na_2O \cdot Sb_2O_5 \cdot 22V_2O_5$

The general pharmacological action of vanadium has been established by the fundamental work of Priestley, Gamgee and Larmuth, and more recently by the valuable contributions of Jackson, therefore, the action of the above mentioned salts on the respiration, blood pressure, muscle, and nervous system was not determined.

The following investigations were conducted:

The toxicity of the vanadium salts was determined in the following animals: horses, sheep, rabbits, guinea pigs, rats, mice, pigeons, chickens, frogs, and fishes. In the earlier work, sodium tetravanadate was found to be the most stable and least toxic vanadium salt, easily soluble in water and of a neutral action, which in lower concentrations could be readily sterilized. This salt was used to investigate the action of vanadium on infusoria, bacteria, yeast, protozoa, plants, nematodes, enzymes, and toxins. The close relationship of vanadium to arsenic warranted an extensive investigation of the different vanadium salts as such, and also in combination with other known antiprotozoic agents in experimental trypanosomiasis and spirochetosis (recurrent fever and syphilis).

The action of vanadium on the circulating blood cells was studied on rabbits as well as in a case of myelogenous leukemia. The distribution of vanadium in chronic and acute poisoning was determined, as well as the excretion and influence on the metabolism in normal human beings. A careful macroscopical and microscopical examination was made of all animals poisoned by vanadium. The experimental findings suggested a clinical trial of vanadium particularly in syphilis.

#### CHEMICAL

Vanadium is a member of the therapeutically active fifth group of the periodic system in which we find nitrogen, phosphorous, arsenic, antimony, and bismuth. It is the first member of the subgroup, and has an atomic weight of 51.2, intermediate between that of phosphorous 31 and arsenic 75. It is also on a line with titanium, chromium, manganese, and iron. Chemically, vanadium is related to phosphorus and arsenic and, in a lesser degree, to manganese and iron. Vanadium follows nitrogen very closely in its oxides, and forms compounds in which it shows a valence from two to five. In the lower valences vanadium is purely metallic in character. With the increase in valence, the metallic character is lost and acidic properties acquired, so that in the pentad state (vanadium pentoxide) the metal-



lic properties have disappeared and we have a true acid oxide closely related in its chemical behavior to the analogous oxides of phosphorous and arsenic.

On account of their affinity for oxygen and, therefore, their rapid oxidation, the lower oxides and their salts are not suitable for therapeutic purposes. Salts in which the vanadium has a valency of four or five appear to be the best adapted for this use.

The acids derived from the pentoxide of vanadium closely follow those of phosphorus and arsenic. A larger number, however, is formed, due to the tendency to form more complex aggregations than is the case with phosphorus or arsenic. Some of these are derived from the pentoxide, and others from both the pentoxide and tetroxide. The following graphic formulas clearly demonstrate the relationship of the different vanadic acids and show that these differ only in the degree of hydration of the oxide.

#### TOXICITY OF VARIOUS VANADIUM SALTS

Previous investigations on the toxicity of vanadium were confined to but a few animals. Sodium orthovanadate was the salt commonly used. Gamgee and Larmuth studied the action of the orthovanadate, metavanadate, and pyrovanadate of soda on frogs and rats without giving animal weights, so that a definite toxicity could not be stated. Priestley gave the fatal dose of vanadium pentoxide, administered intravenously as sodium orthovanadate, as 10 mg. per 1000 gm. of rabbit. Jackson gave no data as to the toxicity of the orthovanadate.

In order to definitely establish the toxicity of the various vanadium salts, various warm-blooded animals were used. The following tables give the toxicities in milligrams of vanadium pentoxide per kilogram of animal weight:

TABLE II

RABBITS	
Intravenous Injection	
<i>Salt</i>	<i>V<sub>2</sub>O<sub>5</sub> in mg. per 1000 gm.</i>
Colloidal Vanadium Pentoxide	1 - 2
Ammonium Metavanadate	1.5- 2
Sodium Orthovanadate	2 - 3
Sodium Pyrovanadate	3 - 4
Sodium Tetravanadate	6 - 8
Sodium Hexavanadate	30 -40
Copper Tetravanadate	2 - 3
Vanadyl Sulphate	18 -20
Ammonium Vanado-arsenate	8.5-10
Ammonium Vanadi-arsenate	2 - 3
Sodium Stibinivanadate	5 - 7

## GUINEA PIGS

Subcutaneous Injection		
<i>Salt</i>	<i>Per 100 gm.</i>	
Ammonium Metavanadate		1- 2
Sodium Orthovanadate		1- 2
Sodium Pyrovanadate		1- 2
Colloidal Vanadium Pentoxide	2 -2.8	20-28
Aniline Vanadate	1 -2	10-20
Sodium Vanadite	3 -4	30-40
Sodium Tetravanadate	1.8-2	18-20
Vanadyl Sulphate	3.5-4.5	35-45
Sodium Hexavanadate	4 -5	40-50

## RATS

Subcutaneous Injection		
<i>Salt</i>	<i>Per 100 gm.</i>	<i>Per 1000 gm.</i>
Ammonium Metavanadate	2 - 3	20- 30
Sodium Pyrovanadate	4 - 5	40- 50
Sodium Orthovanadate	5 - 6	50- 60
Sodium Vanadite	1 - 2	10- 20
Sodium Tetravanadate	3 - 4	30- 40
Copper Tetravanadate	4.5- 5.5	45- 55
Aniline Vanadate	4 - 5	40- 50
Sodium Hexavanadate	4 - 5	40- 50
Vanadyl Sulphate	15.8-19	158-190
Ammonium Vanado-arsenate	2.8- 3.2	28- 32
Ammonium Vanadi-arsenate	1.2- 1.5	12- 15
Antimony Vanadate	4 - 5	40- 50

## MICE

Subcutaneous Injection		
<i>Salt</i>	<i>Per 20 gm.</i>	<i>Per 1000 gm.</i>
Ammonium Metavanadate	0.5-1	25 - 50
Sodium Pyrovanadate	1 -2	50 -100
Sodium Orthovanadate	1 -2	50 -100
Sodium Vanadite	2 -3	100 -150
Sodium Tetravanadate	.5-1	25 - 50
Sodium Hexavanadate	2 -3	100 -150
Mercury Tetravanadate	.1- .15	5 - 7.5
Aniline Vanadate	1.5-2	75 -100
Vanadyl Sulphate	2.5-3	125 -150
Colloidal Vanadium Pentoxide	1.75-2.35	87.5-117.5

## HORSES

Intravenous Injection	
<i>Salt</i>	<i>Per 1000 gm.</i>
Sodium Tetravanadate	4.4

## CHICKENS

Intramuscular Injection	
<i>Salt</i>	<i>Per 1000 gm.</i>
Sodium Tetravanadate	15-20

## PIGEONS

Intramuscular Injection	
<i>Salt</i>	<i>Per 1000 gm.</i>
Sodium Tetravanadate	9-10



## FROGS

Injection Into Anterior Lymph Sac		
Salt	Per 100 gm.	Per 1000 gm.
Sodium Tetravanadate		
Rana Temporaria	5	50
Rana Catesbiana	5-6	50-60

## MAXIMUM AND MINIMUM TOXICITY OF THE DIFFERENT VANADIUM SALTS FOR DIFFERENT ANIMALS PER 1000 GM.

Most Toxic		Least Toxic	
Rabbits	Colloidal Vanadium Pentoxide (1-2) Ammonium Metavanadate (1.5-2)	Sodium Hexavanadate (30-40) Vanadyl Sulphate (18-20)	
Mice	Mercury Tetravanadate (5-7.5) Sodium Tetravanadate (25-50) Ammonium Metavanadate (25-50)	Vanadyl Sulphate (125-150) Sodium Vanadite (100-150) Sodium Hexavanadate (100-150)	
Guinea Pigs	Aniline Vanadate (10-20) Ammonium Metavanadate (10-20) Sodium Pyrovanadate (10-20) Sodium Orthovanadate (10-20)	Sodium Hexavanadate (40-50) Vanadyl Sulphate (35-45)	
Rats	Sodium Vanadite (10-20) Ammonium Metavanadate (20-30) Ammonium Vanadi-arsenate (12-15)	Vanadyl Sulphate (158-190)	

The toxicities of the different vanadium salts as given in the foregoing tables can be viewed only as relative, but not as absolute values. Individual resistance, nutrition, absorption, and other unknown factors render the exact estimation of toxicity an extremely difficult matter. Undoubtedly, the intravenous injection of a substance is the most ideal way to determine toxicity, since an immediate and general distribution takes place without local fixation, partial or delayed absorption, chemical change or too rapid elimination. For this reason preference has been given to the toxicities determined on rabbits by intravenous injection. The results obtained by intramuscular or subcutaneous injection in the other animals corroborate the rabbit findings. Toxicity estimations by mouth were not attempted since too many uncontrollable factors were involved.

The above tables show that ammonium metavanadate is the most toxic of the vanadium salts investigated, while the hexavanadate and vanadyl sulphate are the least toxic. Contrary to the findings of Larmuth and Gamgee, the metavanadate is the most toxic, the orthovanadate intermediate and the pyrovanadate the least toxic for rabbits. Sodium tetravanadate with a toxicity of 6-8 mg., vanadyl sulphate 18-20 mg., follow the pyrovanadate in order of toxicity. Sodium hexavanadate 30-40 mg. is the least toxic.

The toxicity of the vanadium salts appears to depend on their chemical constitution and is influenced by the presence of hydroxyl and double bonded oxygen. A study of Table I shows the following:

Colloidal vanadium pentoxide has five hydroxyl groups to one vanadium atom; orthovanadic acid three hydroxyls and a single double bonded oxygen to one vanadium atom; metavanadic acid has a single hydroxyl, but two double bonded oxygens to one vanadium atom; pyrovanadic acid has two hydroxyls and one double bonded oxygen to each vanadium atom; tetravanadic acid has two hydroxyls on two vanadium atoms and two double bonded oxygens on each of the remaining two vanadium atoms; hexavanadic acid has a hydroxyl group on four vanadium atoms and a single double bonded oxygen on each of the six vanadium atoms.

A consideration of these facts points to the conclusion that the toxicity of a vanadium salt depends on the following factors:

1. The number of hydroxyl groups attached to a vanadium atom.
2. The presence of the  $\text{VO}_2$  group.

The colloidal pentoxide is most toxic with the five hydroxyl groups to a single vanadium atom. Metavanadic acid is next with the toxic  $\text{VO}_2$  group and but one hydroxyl to the vanadium atom. Orthovanadic acid follows in toxicity with three hydroxyls to one vanadium atom, but without the two oxygen atoms on the same vanadium atom. Pyrovanadic acid is still less toxic with but two hydroxyls to a vanadium atom and like the orthovanadic acid without the ( $\text{VO}_2$ ) complex. Tetravanadic acid has but two hydroxyls on two of the four vanadium atoms, which decreases the toxicity, but at the same time two ( $\text{VO}_2$ ) groups are present, but free of hydroxyl. These latter groups counteract the lessened toxicity due to the low ratio of the hydroxyl groups to the number of vanadium atoms (1-2) and give tetravanadic acid a toxicity which is the resultant of the diminished toxicity due to the low hydroxyl ratio with the enhanced toxicity due to the ( $\text{VO}_2$ ) complex.

Hexavanadic acid, the least toxic of the acids studied, has four hydroxyls to six vanadium atoms without the  $\text{VO}_2$  complex, and, therefore, has a diminished toxicity due to the low hydroxyl ratio without any increase due to the toxic  $\text{VO}_2$  group. In addition to the role played by hydroxyl and the  $\text{VO}_2$  complex in the simpler acids, it appears that with the increase in the number of vanadium atoms to produce the more complex acids, the toxicity diminishes, since these

acids are condensation products of the simpler acids formed by the elimination of water, thereby causing a diminution in the ratio of hydroxyl to vanadium. As long as this ratio is reduced without the formation of the  $\text{VO}_2$  complex, the toxicity is reduced correspondingly, but if the  $\text{VO}_2$  group is present, the final toxicity is the resultant of the diminished toxicity due to the low hydroxyl ratio, with the increased toxicity, due to the  $\text{VO}_2$  group as in tetravanadic acid.

The single double bonded oxygen apparently diminishes toxicity, as is demonstrated in the case of hexavanadic acid, vanadous acid and vanadyl sulphate. The bridge or linking oxygen is probably inert and can be considered only as the anhydride of two hydroxyls which are thus rendered atoxic.

#### GENERAL SYMPTOMATOLOGY OF VANADIUM POISONING

In order to establish as far as possible the symptoms and effects of vanadium poisoning, experiments on various lower and higher animals were made, with the following results:

**WORMS.**—If worms (*lumbricus terrestris*) are immersed in a weak solution of sodium tetravanadate (0.5 to 1%  $\text{V}_2\text{O}_5$ ) a marked increase in their activity compared to controls kept in 0.85% salt solution is observed. This increased activity may last for several hours, and is followed by an evacuation of the intestinal canal. The same action is observed for a short time in more concentrated solutions (5 to 12½%  $\text{V}_2\text{O}_5$ ) but the vigorous muscular contraction is quickly lessened, then completely paralyzed.

**FISH.**—In a solution of sodium tetravanadate containing from 5 to 12½%  $\text{V}_2\text{O}_5$ , gold fish (*carassus auratus*) exhibit a marked excitation. Increased respiration is indicated by the quickened movement of gills. As the vanadium is absorbed the excitation decreases, the respiration grows weaker, the fish lies on its side, and comes to the surface of the fluid. The final termination of life is marked by slight convulsions and gasping with mouth opened wide. Hemorrhages from the gills are observed shortly before respiration ceases. After the cessation of respiration the muscle tissue responds to electric stimulation.

**FROGS.**—On injecting frogs (*Rana temporaria* and *Rana catesbiana*) with a solution of sodium orthovanadate, Jackson immediately observed great excitement, agitation, and convulsions before absorption of the salt was possible. When the drug was absorbed, Priestley noted

that the respiratory muscles were the first to cease their action. Consciousness remained for some hours after the cessation of respiration until a gradual and progressive depression and paralysis set in, finally ending in death. The heart action, voluntary muscles, and motor nerves do not appear to be directly affected since the muscular and nervous irritability remained perfect to electrical stimulation. Our experiments confirm the latter findings, but we have not observed the violent symptoms immediately after injection. These must undoubtedly be due to the free alkali always present in an aqueous solution of sodium orthovanadate. Frogs injected with a neutral vanadium salt like sodium tetravanadate, do not exhibit any extraordinary symptoms, but exhibit normal behavior until depression and paralysis set in.

**BIRDS.**—The first symptoms of vanadium poisoning in pigeons and chickens are drowsiness, and action on the alimentary canal. Vomiting and a free discharge of fecal matter, first normal and later hemorrhagic in character, follows. The respiration, increased at first, becomes more feeble and shallow, and finally results in intermittent gasping. The animal sprawls; the legs and body appear to be paralyzed; and death ensues. In pigeons an average drop in temperature of  $4^{\circ}$  F. was noted just before death.

**MAMMALS.**—In the lower mammals, such as mice, rats, guinea pigs, and rabbits, vanadium in acute fatal doses acts chiefly upon the central nervous system. Depression, somnolence, convulsions, weakness, and finally paralysis are the main symptoms. The intravenous injection of large doses of vanadium in rabbits causes respiratory paralysis. In acute vanadium poisoning, hyperemia, especially of the lungs and abdominal organs, is noted. In subfatal doses the lungs, kidneys, and liver are mainly affected, and the alimentary canal to a lesser degree. Edema, hemorrhages, inflammation of the lungs, and nephritis are the causes of death.

In dogs, Priestley found that relatively large doses of vanadium failed to produce any nervous symptoms, while intense gastric and intestinal disturbances, vomiting, abdominal pain, and hemorrhagic discharge from the intestines during life gave immediate indications of the cause of death. In cats, Priestley noted nervous symptoms (convulsions), as well as signs of intestinal irritations.

A sheep, which received 230 mg.  $V_2O_5$  in the form of sodium tetra-

vanadate in fifty-one days, exhibited the following symptoms: Colic, diarrhea, loss of appetite, progressive weakness, and emaciation.

Horses injected with large doses of vanadium (1 gm. to 2.6 gm.  $V_2O_5$ ) intravenously, exhibited a free discharge of fecal matter, abdominal colic, sweating, increased respiration, and muscular weakness. These initial symptoms usually endure for about an hour and are followed in eight hours by a marked diarrhea of a hemorrhagic character, edema and hemorrhages of the lungs, and a general paralysis which causes death.

In man after the intravenous injection of 20 mg.  $V_2O_5$  in the form of sodium tetravanadate, the following symptoms have at times been observed: constriction of the throat, salivation, lachrymation, disappearance of pulse, free discharge of feces, vomiting, cessation of respiration, and a drop of three degrees in the temperature. Dutton reported on chronic industrial vanadium poisoning caused by the inhalation of crude oxides and salts of vanadium as follows: One of the most characteristic and prominent symptoms appears to be a dry hacking and irritating cough. Pulmonary hemorrhages are frequent and severe and may cause death. Other symptoms are loss of appetite, persistent diarrhea followed by obstinate constipation, anemia, emaciation, and nervous disturbances. Albuminuria and hematuria seem to be frequently observed. In fatal cases the lungs are highly congested and show a marked destruction of alveolar epithelium, besides acute hemorrhagic nephritis and gastroenteritis.

#### THE ACTION OF VANADIUM ON PLANTS, YEAST, LOWER ORGANISMS, ENZYME AND TOXINS

PLANTS.—Priestley stated that the germination of mustard and lettuce seeds were totally prevented in a 1%  $V_2O_5$  solution. A concentration of .1% or less of  $V_2O_5$  did not markedly interfere with germination. Suzuki found that 0.001% of vanadium sulphate exerted a very harmful action on the germination of barley, while 0.0001% had no influence. He could not confirm the findings of Witz and Osmond, who claimed stimulating properties for vanadium. In our experiments concentrations from 0.2% to 0.05%  $V_2O_5$  were markedly injurious to growth, 0.02% to 0.006% exerted an inhibitory influence while 0.003% to .0003% had no influence.

The close relationship of vanadium to phosphorus and its occur-

rence in coal\* and plant ashes suggested experiments to determine if vanadium could be substituted for phosphorus. The following nutrient solution was used for three controls in numbers 1, 2 and 3:

Ca(NO <sub>3</sub> ) <sub>2</sub>	1. gm.
MgSO <sub>4</sub>	.25 gm.
K H <sub>2</sub> PO <sub>4</sub>	.025 gm.
Fe	Trace

Numbers 4 and 5 were the same as the controls, plus .025 gm. K<sub>2</sub>V<sub>4</sub>O<sub>11</sub>. Numbers 6 and 7 were the same as 1, 2 and 3, but free of phosphorus with vanadium substituted for it. Numbers 8 and 9 were the same as 1 and 2, but free of iron and phosphorus, and vanadium substituted for them. Sprouted wheat seedlings were immersed in wide test tubes containing the above nutrient media and placed in the sunlight.

The accompanying photograph shows that the vanadium not only cannot replace the phosphorus, but that it is injurious to growth.

**SACCHAROMYCES CEREVISIÆ.**—Yeast exhibits a most surprising resistance to vanadium. Up to a concentration of 5% V<sub>2</sub>O<sub>5</sub> fermentation proceeds as rapidly as with the control. Above 5% the fermentation takes place, but not so rapidly as with the lower concentrations. The fermentation continues up to 10% V<sub>2</sub>O<sub>5</sub>. It was impossible to obtain a greater concentration on account of the solubility limit of the salt.

**BACTERIA.**—Priestley mentioned briefly that sodium orthovanadate in one-half per cent solution does not prevent the development of bacteria without reference to the strain used. Lyonnet, Martz and Martin, and also Jackson, found that sodium metavanadate in a dilution of one to a thousand had no bactericidal action. In comparison with the organic and inorganic germicides, vanadium shows selective but not general germicidal properties. Experiments were carried out with sodium tetravanadate on a number of pathogenic bacteria, with the following results, concentrations expressed in terms of V<sub>2</sub>O<sub>5</sub>:

*Streptococci.*—Three strains used; all killed in 0.4% solution in seven days. One strain from the throat of a scarlet fever case was sterile in a 0.2% solution in three days.

*Staphylococci.*—Pneumococci, meningococci, diphtheria, tetanus,

\*Demarcay found spectroscopically, that the ash of the pine, grapevine, oak, poplar, beech, and whitefir, contained vanadium. The ash of coal found in Argentina and Peru contains as high as 38% V<sub>2</sub>O<sub>5</sub>.

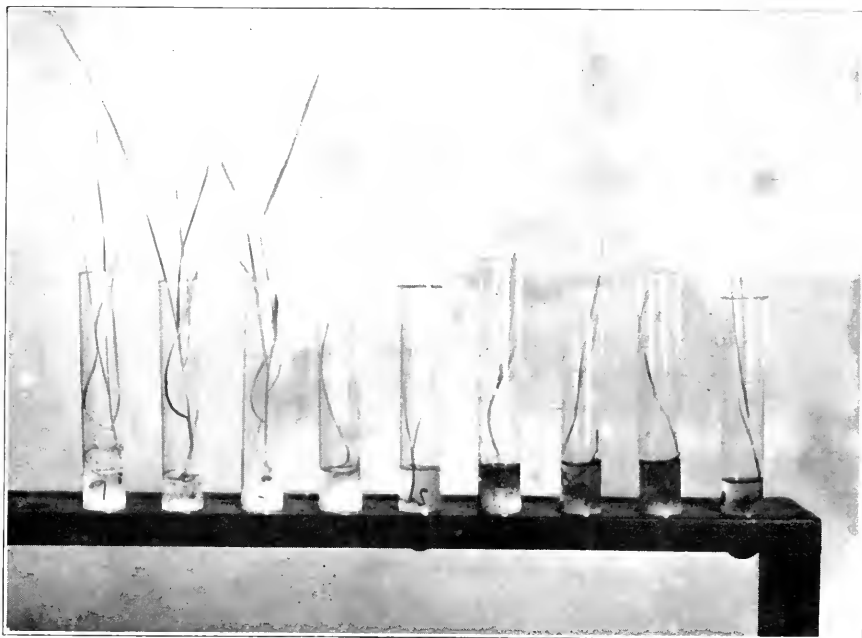


Fig. 1.—Effect of vanadium on plant growth.





anthrax, and malignant edema bacilli not killed in 0.8% solution in five days.

*Cholera bacilli*.—Six strains used; all sterile in 0.2% solution in four days.

*Typhoid bacilli*.—Four strains used; all sterile in 0.5% solution in four days. Three strains killed in 0.4% solution in two days.

*Dysentery bacilli*.—Four strains used; three sterile in 0.4% solution in two days, and one in 0.5% in two days.

*Enteritis bacilli*.—Three strains used; all killed in 0.6% solution in two days.

*Pyocyaneous*.—Nine strains used; four killed in 0.4% solution, two in 0.5% solution, two in 0.7% solution, and one in 0.8% solution in five days.

*Diplococcus Melitensis*.—One strain killed in 0.2% solution in two days.

*Human tubercle bacilli*.—Grow on culture medium up to 2%  $V_2O_5$ . Tubercle bacilli immersed in a 5% solution of  $V_2O_5$  were still living at the end of four weeks. Several fungi such as *aspergillus glaucus* showed the same resistance to vanadium. Cholera, typhoid, and dysentery bacilli appear to be more readily killed, while the remainder in a concentration of 0.2% to 0.8%  $V_2O_5$  solution are either not killed, or require several days for sterilization depending on the strain used.

In animal experiments sodium tetravanadate had neither a preventative nor a curative effect on experimental pneumococcal or streptococcal infections in mice. The same was found in experimental tuberculosis in rabbits and guinea pigs. Several hundred tubercular guinea pigs in all stages of the disease were fed and injected with different vanadium salts, without influencing the tubercular process, since all the pigs under treatment died in about the same time as the controls. The same results were obtained with tubercular rabbits injected with sodium tetravanadate.

**INFUSORIA**.—*Opalina ranarum* harboring in the frog's rectum was used in these experiments. For purposes of comparison with vanadium the following salts were tested: uranium nitrate, potassium antimonyl tartrate, sodium chromate, sodium arsenate, and the double acids of vanadium with arsenic and antimonious oxides. Normal salt solution containing *Opalina ranarum* was mixed with the proper amount of the various chemicals to give the desired concentration

and then examined under the microscope. The fatal dose as given in Table III is that concentration by which the vital function was immediately impaired.

TABLE III

			FATAL DOSE
Sodium Tetravanadate	as	$V_2O_5$	12.1 %
Uranyl Nitrate	"	$U_2O_5$	0.02%
Sodium Arsenate	"	$As_2O_5$	1.0 %
Sodium Chromate	"	$CrO_3$	2 %
Potassium Antimonyl Tartrate	"	$Sb_2O_3$	1.7 %
Ammonium Vanado-arsenate	"	$V_2O_5$	.10%
Ammonium Vanadi-arsenate	"	$V_2O_5$	.36%
Sodium Stibinivanadate	"	$V_2O_5$	.02%

These experiments show that vanadium as such is atoxic for *Opalina ranarum*. There is no doubt that the death of this infusorian in a solution of sodium tetravanadate containing 12.5%  $V_2O_5$  is due to osmotic disturbances, and not to any inherent toxicity of vanadium.

Priestley found that 0.01% of  $V_2O_5$  in the form of sodium orthovanadate caused an immediate disturbance of the vital functions of infusoria developed from an infusion of cabbage leaves. This high toxicity was caused undoubtedly by the alkali formed by hydrolysis when sodium orthovanadate is dissolved in water and not by the vanadium. This is readily shown by the work of U. Korentschewsky who found that infusoria are extremely sensitive to minute traces of free alkali.

The complex acids of vanadium formed by the union of vanadic pentoxide with other acid oxides are far more toxic than the simple tetravanadate and are also more toxic than the arsenate and chromate of sodium, but, with the exception of the stibinivanadate, not as toxic as uranyl nitrate.

#### TRYPANOSOMES AND SPIROCHETES

Thus far the elements arsenic and antimony, of the fifth group of the periodic system of the elements, have been the most effective in the treatment of protozoic diseases. Noelt and Mayer mention vanadium as a trypanocidal agent, but cite neither experimental data nor references. It was impossible to find any other references to the literature in regard to the use of vanadium in protozoic diseases.

The action of vanadium was studied in experimental trypanosomiasis (*Trypanosoma equiperdum* and *brucei*) and spirochetosis (spiro-

chete novyi, American recurrens, and spirochete pallida). The experiments with trypanosomiasis were conducted with guinea pigs and mice infected with trypanosoma brucei, and with rats and mice infected with trypanosoma equiperdum. The experiments with spirochetes were studied on rats infected with spirochete Novy and on rabbits with serotum syphilis.

#### EXPERIMENTS ON TRYPANOSOMIASIS

In the following tables a summary is given of the experiments on the action of the simple and more complex vanadium salts, as well as of the action of the other known trypanocidal agents, as arsacetin, salvarsan, and trypan red and combinations of the three latter with vanadium.

The simple vanadium salts such as sodium tetravanadate, aniline vanadate, and vanadyl sulphate suppress the multiplication of trypanosoma brucei, or temporarily inhibit the course of the disease. A complete sterilization, however, could not be accomplished and the animals finally succumbed to the infection. It seems that a vanadium tolerance must be established as is the case with arsenic, antimony and organic dyes. The action of these salts in effecting a temporary sterilization is analogous to the action of arsacetin.

The complex vanadium compounds, such as ammonium vanadi-arsenate, accomplishes a complete sterilization in about 16.6% of the infected animals, while ammonium vanado-arsenate and sodium phosphovanadate are without effect. The combination of aniline vanadate and arsacetin accomplishes a complete sterilization in about 50% of the animals and is almost as effective as salvarsan alone, giving a sterilization of almost 60%. Experiments on guinea pigs infected with trypanosoma brucei show that vanadium alone does not lead to complete sterilization. The animals under treatment outlived the controls by 20 to 25 days.

In the case of mice a combination of arsacetin and vanadium accomplished a complete sterilization in 65% to 100% of the animals treated. The following tables give the result of the combined treatment with one or two vanadium salts with arsacetin alone or together with trypan red and salvarsan.

TABLE IV  
TRYPANOSOMA MICE

TREATMENT	CONTROL ANIMALS			ANIMALS TREATED			Cures in % of total treated
	Amount injected pro die to 20 gm. weight	No. of animals	Average length of life	No. of animals	Average length of life	Longest period of life.	
Aniline Vanadate $\frac{1}{2}$ -2 mg.		8 mice	$3\frac{1}{2}$ days	26 mice	6 days	31 days	Still living % of cures
Sodium Tetravanadate $\frac{1}{2}$ -5 mg.		7 mice	$4\frac{1}{2}$ days	33 mice	$8\frac{1}{2}$ days	25 days	None
Arsacetin $\frac{1}{2}$ -. $\frac{3}{4}$ mg.		3 mice	$4\frac{3}{4}$ days	16 mice	$10\frac{1}{2}$ days	27 days	None
Trypan red 5 mg.		1 mouse	4 days	4 mice	8 days	17 days	None
Vanadyleitrate 2 mg.		None	None	2 mice	7 days	10 days	None
Arsacetin 1 mg.							None
Sodium Tetravanadate .5 mg.		None	None				None
Aniline Vanadate $\frac{1}{2}$ mg.		1 mouse	4 days	4 mice	$10\frac{1}{2}$ days	23 days	None
Phosphovanadic acid 1.5 mg.				3 mice	$5\frac{1}{2}$ days	11 days	None
Salvarsan 5 mg.							None
Sodium Tetravanadate $\frac{1}{4}$ mg.		2 mice	3 days	3 mice	$16\frac{1}{2}$ days	35 days	None
Aniline Vanadate 1 mg.					(5 mice)		None
Ammonium Vanadi-arsenate 1 mg.		1 mouse	6 days	6 mice	$16\frac{1}{2}$ days	1 year	1 mouse 16.6%
Ammonium Vanado-arsenate $\frac{1}{2}$ -1 mg.		1 mouse	6 days	7 mice	$7\frac{1}{2}$ days	13 days	None
Salvarsan		1 mouse	4 days	3 mice	62 days	1 year	2 mice 33%
Arsacetin 2 mg.					55.5 days	(2 mice)	
Aniline Vanadate 1 mg.		1 mouse	4 days	4 mice	(2 mice)	1 year	2 mice 50%

TABLE V  
TRYPANOSOMA GUINEA PIGS

TREATMENT	CONTROL	NUMBER OF ANIMALS TREATED	STILL LIVING	CURES IN % OF TOTAL TREATED
Amount injected pro die to 250 gm. weight	Average length of life			
<i>No. 1.</i>				
Arsacetin 5-10 mg.	5 days.	32 pigs.	5 pigs.	15.06%
Sodium Tetravanadate $\frac{1}{2}$ -3 mg.				
Aniline Vanadate 2 mg.				
<i>No. 2.</i>				
Arsacetin 5 mg.	5 days.	1 pig.	1 pig.	100%
Sodium Tetravanadate 3 mg.				
Prophylactic.				
<i>No. 3.</i>				
Arsacetin 5 mg.	5 days.	2 pigs.	2 pigs.	100%
Sodium Tetravanadate 2 mg.				
Aniline Vanadate 2 mg.				
Prophylactic.				
<i>No. 4.</i>				
Arsacetin 5-10 mg.	5 days.	23 pigs.	10 pigs.	43.4%
Sodium Tetravanadate 1-3 mg.				
<i>No. 5.</i>				
Arsacetin 5 mg.	6 days.	12 pigs.	3 pigs.	23%
Sodium Tetravanadate 2 mg.				
Aniline Vanadate 2 mg.				
Trypan red 10 mg.				
<i>No. 6.</i>				
Salvarsan 10 mg.	5 days.	2 pigs.	2 pigs.	100%
<i>No. 7.</i>				
Arsacetin 5 mg.	5 days.	20 pigs.	15 pigs.	75%
Sodium Tetravanadate 2 mg.				
Aniline Vanadate 2 mg.				
Salvarsan 10 mg.				

From the foregoing tables it is evident that the curative treatment with a combination of sodium tetravanadate with arsacetin gives complete sterilization in 92% of the animals, while the combination of two vanadium salts as aniline vanadate and sodium tetravanadate with arsacetin alone or with trypan red gives a complete sterilization in 65% to 69% only, while in conjunction with salvarsan, 90% of the animals can be saved. None of the combinations accomplish a complete sterilization of 100% as with salvarsan alone. On the other hand arsacetin and sodium tetravanadate or aniline vanadate given as a prophylactic protect 100% of the animals against infection.

While trypanosoma brucei is influenced by vanadium, trypanosoma equiperdum is most resistant. Numerous experiments with rats and mice show that the simple vanadium salts as well as the more com-

plex salts, with arsenic, antimony, and copper exert no effect, the animals dying in the same time as the controls.

#### EXPERIMENTS ON SPIROCHETES

Vanadium has no effect on rats infected with spirochete novyi. The number of the microorganisms is not decreased nor is the life of the animal prolonged.

The influence of vanadium on spirochete pallida was studied on well developed scrotum syphilis of rabbits, when repeated examination of the chancre showed the presence of spirochetes. All examinations were made with the dark-field illuminator.

Syphilitic keratitis, as well as orchitis syphilitica, is not well adapted for chemotherapeutic studies. Scrotum syphilis is most convenient, and is very similar to the primary chancre in man. If a small piece of syphilitic testis tissue is inoculated beneath the scrotum, in about three or four weeks a slowly growing reddish infiltration about the size of a lentil is noticed. This may develop to the size of a pea or grow as large as a small hazelnut. In six or eight weeks the infiltration begins to ulcerate, and forms a dry scab. On removal of the scab, a sharply outlined ulcer with hard indurated edges extending above the healthy skin is evident. The ulcer may grow to almost the size of a quarter. Such a chancre may exist for five months or longer, with a tendency to partial healing, followed by further ulceration. If the chancre extends to the testicle, a typical orchitis syphilitica may develop with an enlargement of the inguinal glands. The entire testicle may be uniformly indurated or movable hard nodules may develop sometimes the size of an almond, leaving the skin intact. On section these nodules are of a tough caoutchouc consistency, yellowish white in color, their centers necrotic, containing a thick greyish, viscid liquid with numerous spirochetes. The nodules may in time fuse with the scrotal skin and develop into an ulcer.

The vanadium salts used were sodium tetravanadate, sodium hexavanadate and vanadyl sulphate all injected intravenously. The amounts injected were two-thirds of the fatal dose. The animals treated were examined daily for spirochetes, and the course of the disease carefully noted. The following protocol is a typical example of a syphilitic rabbit treated with sodium tetravanadate.

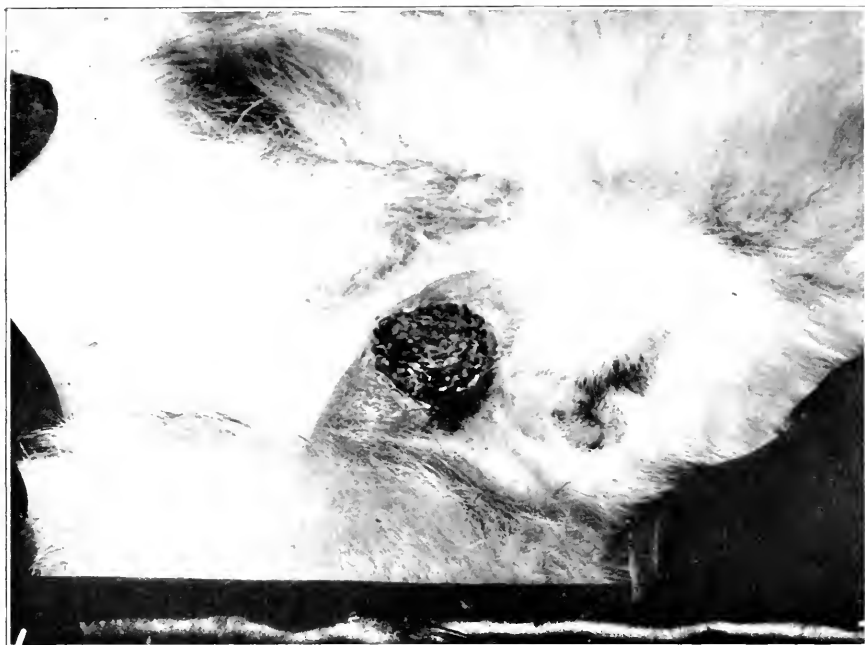


Fig. 2.—Scrotum syphilis of rabbit before treatment.



Fig. 3.—Scrotum syphilis of rabbit three days after injection of 10 mg.  $V_2O_5$  as tetravanadate.







Fig. 4.—Testicle showing scar formation, 8 days after the injection of 14 mg.  $V_2O_5$  as tetravanadate.



Rabbit No. 2, first series, right testicle infected February 10, 1916.

March 9, 1916.—Testicle shows ulcer about 15 mm. in diameter with indurated edges, covered with a dry scab. Numerous spirochetes. Weight 2230 grams. 5 mg.  $V_2O_5$  intravenously.

March 10, 1916.—Few spirochetes. No appreciable change in chancre. Induration perhaps lessened. 5 mg.  $V_2O_5$  intravenously.

March 11, 1916.—Scab of ulcer fallen off. Induration less. No spirochetes.

March 12, 1916.—No spirochetes. Ulcer half reduced in size. Induration still present. 4 mg.  $V_2O_5$  intravenously.

March 13, 1916.—No spirochetes. Induration softer. Chancre reduced in size.

March 14, 1916.—No spirochetes. Ulcer about pinhead in size. Induration almost disappeared.

March 17, 1916.—Ulcer entirely healed, leaving a small bluish white scar.

April 17, 1916.—Rabbit died spontaneously. Autopsy did not show cause of death. Microscopic examination of the testicle showed that the syphilitic inflammation had entirely healed, leaving a fibrous indurated area in place of the ulcer in which spirochetes could not be found by Levaditi's method.

The same results were obtained with vanadyl sulphate and sodium hexavanadate. The latter proved to be the most effective, since a single injection of 20 to 25 mg.  $V_2O_5$  per 1000 gm. caused a disappearance of the spirochetes within 24 hours. At present, it can not be definitely stated if a single large dose of the hexavanadate causes complete sterilization. Many of our valuable animals which were treated succumbed to secondary infections. It appears that the latent secondary infections, especially with a diplococcus and pseudotuberculosis, both of which were very prevalent this year, make rabbits very sensitive to vanadium. The toxic dose of vanadium for such animals is far below that for a healthy rabbit.

These experiments prove that vanadium has a marked effect on spirochete pallida, and is capable of curing experimental syphilis in rabbits. It seems that this property is a function of the amount of vanadium injected and is independent of the constitution of the vanadium salt used. Of course, for therapeutic purposes the least toxic vanadium salt should be chosen.

*Enzymes.*—The therapeutic administration of vanadium per os suggested an investigation of its effect upon the digestive enzymes. The typical enzymes, pepsin and pancreatin, were used. The method for the assay of pepsin as laid down in the United States Pharmacopeia, Eighth Revision, was followed to determine the influence of vanadium on the proteolytic activity of this enzyme. The pharmacopeial method for the valuation of pancreatin by means of starch was followed to determine the influence of vanadium on the amylolytic activity of the pancreatin. Instead of the iodine test for the determination of the

completion of the hydrolysis of the starch, the amount of glucose formed was determined and used as the measure of pancreatic action.

A concentration of 0.2% of  $V_2O_5$  in the form of sodium tetravanadate completely inhibits the proteolytic activity of pepsin, as well as the amylolytic activity of the pancreatin. Since vanadium does not precipitate albumin in neutral or in slightly alkaline solutions, the enzymes, pancreatin, and pepsin must be directly affected by the vanadium. This is rather unexpected since the production of invertase by yeast is but slightly influenced in stronger concentrations, and apparently not at all in 0.2%  $V_2O_5$ .

*Toxins.*—The early French investigators claimed that vanadium by virtue of its property as a carrier of oxygen, had a destructive effect on toxins. The following experiment showed this claim to be unfounded:

Diphtheria and tetanus toxins were carefully standardized, and the fatal dose determined. The fatal dose of tetanus toxins plus 0.25 mg. of  $V_2O_5$  in the form of sodium tetravanadate was diluted to 1 c.c. volume with normal salt solution, and incubated at 37° C. for 5 hours. Tetanus toxin diluted with salt solution was treated in a similar way as a control. Seven mice were then injected, three with the vanadium tetanus toxin, three with tetanus toxin, and one with 0.25 mg.  $V_2O_5$ . With the exception of the last mouse, all the animals died in four days of typical tetanus poisoning.

The fatal dose of diphtheria toxin plus 4 mg.  $V_2O_5$  in the form of sodium tetravanadate was diluted to 2 c.c. volume with normal salt solution, and incubated at 37° C. for six hours. Diphtheria toxin diluted with salt solution was treated in a similar way as a control. Seven guinea pigs were then injected, three with vanadium diphtheria toxin, three with the diphtheria toxin, and one with 4 mg.  $V_2O_5$ . With the exception of the last guinea pig, all the animals died in 48 hours of typical diphtheria poisoning.

These experiments disprove the claims made by Helouis and La Tanneur that vanadium is a deintoxicator. The effects noted by Helouis and Le Tanneur were probably due to the acidity of the vanadium solution used, or to the chlorine liberated in their product.

#### GENERAL ACTION OF VANADIUM

*Cardiovascular System.*—There has been a great diversity of opinion as to the influence of vanadium on the cardiovascular system.

Priestley, Larmuth and Gamgee were inclined to believe that some intrinsic nervous mechanism was directly influenced by vanadium and ascribed an action to it similar to digitalis. According to Priestley, there is a temporary diminution of the blood pressure with a tendency to regain its former height. Corresponding to the fall and rise of the blood pressure, there is a diminution in rapidity, and an irregularity of the pulse is observed. At the same time there is a disappearance of the respiratory curves. The rise in blood pressure following the intravenous injection in animals whose cord has been cut was attributed by Priestley to the greater vigor of the heart.

Contrary to this opinion Lyonnet, Martz, and Martin found little influence on the cardiovascular system; while Hallion, Laran, and Luzzato reported a rise in pressure. Hallion and Laran noted a marked irregularity of the heart, as well as a rise in blood pressure. They attributed this action to a marked medullary stimulation since after the section of the vagi nerves, the irregularity ceased. An analogous stimulation of the vasoconstrictor center should cause a rise in blood pressure.

In our experiments with frogs, we found that vanadium injected subcutaneously in moderate and large doses made no appreciable change either in the amplitude or in the beats of the heart as shown by tracings taken directly from the exposed organ. By perfusion of the frog's heart with the vanadium solution a digitalis-like action was observed. The excellent work of Jackson has settled the controversy in regard to the action of vanadium on the cardiovascular system. His conclusions are given verbatim below:

1. When administered intravenously, the chief action of vanadium is expended on the vascular system. The central nervous system has but little influence on this action, for the rise in blood pressure produced by injection of vanadium into an animal whose head had been removed from the body is almost identical both in character and extent with the rise produced by injection of the metal into a normal (etherized animal).

2. With ordinary doses, the mammalian heart is but little affected. The vagus endings in the heart remain active throughout the whole course of intoxication in the intact animal. Batrachian and chelonian hearts seem to be more directly affected by the element than is the mammalian heart.

3. An intense peripheral vasoconstriction is produced by the metal in the spleen, kidneys, and intestines. In the intact animal the cutaneous and muscular vessels dilate from visceral displacement of the blood but in perfusion experiments the limb volume also decreases slightly under the action of vanadium.

4. The view previously held that the rise in general blood pressure was due to a strong stimulation of the medullary vasoconstrictor center is wholly wrong.

5. The peripheral constriction is due to a localized action within the organs themselves. It occurs in a perfectly normal manner in the excised and perfused organs of animals, whose general blood pressure has previously fallen to zero under large doses of the metal.

6. With repeated intravenous injections of the same sized doses into an intact animal, the rise in blood pressure following each injection regularly decreases until at length a fall will be produced by each injection. This is due first to weakening and paralysis of the vasoconstrictor center, and second to a direct depression of the heart.

7. With a moderate dose, the maximum rise in blood pressure will be produced and a further increase in the size of the dose will not give any greater rise in the pressure. This seems due to the fact that a moderate dose gives the maximum contraction of the visceral vessels, and a larger dose does not produce any corresponding constriction of the remaining vessels of the body.

8. The peripheral action of vanadium on the visceral vessels is very much greater than that of barium.

9. With doses of epinephrin and of vanadium so adjusted that each will give the same rise in general blood pressure, the vasoconstriction in the kidney, spleen, and intestine produced by vanadium will be very much greater in extent and duration than that produced by the epinephrin.

10. With moderate (intravenous) injections, the general blood pressure usually returns approximately to its normal level (or even below) several minutes before the constriction in the abdominal organs disappears.

*Respiration.*—Priestley showed that the disturbance of the respiration by vanadium was of centric origin. This conclusion was confirmed by all later investigators. Following the injection of sodium orthovanadate, he found that the respiration was at first stimulated, with an increased rapidity, but with a diminished depth. The increased rapidity declined, followed by a gradual slowing of the respiration until death.

Jackson noted that animals injected subcutaneously with vanadium showed an irregular respiration, becoming slower and finally dyspneic. The dyspnea resembles that produced by aconitine. Cheyne-Stokes respiration was sometimes observed. In the later stages of the intoxication, the respiration becomes more difficult and is finally replaced by deep gasping, which may prolong life for a time. The end of the intoxication is usually marked by a few weak convulsions. After cessation of the respiration, the heart remains beating. According to Jackson's experiments, vanadium causes a constriction of the pulmonary vessels as well as of the bronchi. This action of the metal is wholly peripheral since this phenomenon occurs in animals in which the cervical cord has been sectioned, or the entire head removed. By perfusion of the isolated lung, the same phenomenon is observed. The amount of vanadium necessary to contract the pulmonary vessels is far greater than that required to contract the ves-

sels of the abdominal organs. Epinephrin causes a complete relaxation of the bronchial spasm; atropin also, but to a lesser degree.

Witz and Osmond first called attention to the marvelous oxidizing power of vanadium and suggested its use as an oxygen carrier in the body. According to their theory, vanadium derives oxygen from the oxyhemoglobin forming vanadic or pervanadic acid. The oxygen so derived should be given up to the tissues and hypovanadic acid formed. The latter is reoxidized by the oxyhemoglobin, and vanadic acid again formed. From a chemical standpoint such a reaction does not appear plausible. In the first place, the formation of a pervanadic acid is improbable since this acid is not formed by oxygen alone, but only by peroxides and then in a solution, acid with mineral acid. An acetic acid solution of a vanadate salt does not yield pervanadic acid on the addition of peroxide of hydrogen. As soon as a strong acid, such as nitric or hydrochloric acid, is added the pervanadic acid is at once formed. Furthermore, both Priestley and Jackson have shown that the addition of vanadium salts to oxyhemoglobin does not cause a reduction of the latter to hemoglobin nor is any pervanadic acid formed. Thus far all experiments tend to show that the role of vanadium in the higher animals is not that of an oxygen carrier.\* So far no experiments have been devised to prove beyond doubt that the main action of vanadium rests on its oxidation power. Lyonnet, Guinard, Martz, and Martin tried to prove this by determining the respiratory output of carbon dioxide in guinea pigs when injected subcutaneously with vanadium. Their results are not conclusive; they sometimes obtained an increase, and sometimes a decrease in the carbon dioxide elimination.

Jackson tried to solve the problem by determining the total pulmonary ventilation by means of a spirometer, carefully measuring the volume of the expired air before and after the injection of vanadium, but his results were not conclusive. In about 50% of the cases a slight increase in the total amount of air passing through the lungs was noticed. Jackson does not believe that this is an indication that the oxidizing power of the body is increased. It seems that the

\*The exceedingly interesting investigation of M. Henze, who found that the blood of *Ascidia* (*Phallusia mamillata*) reacts acid and that the blood cells contain 15%  $V_2O_5$ , throws some light on the action of vanadium as an oxygen carrier. While the constitution of this peculiar chromogen is unknown, it must contain the vanadium in the form of a lower oxide since the blood is colorless and on exposure to air turns deep blue. This discovery shows that the vanadium, if present, as an oxygen carrier, can be such only in an acid medium and at the same time precludes such a role in the normal alkaline blood stream since Binz and Schulz have demonstrated that the blood, in their investigation on arsenic, is reducing in its nature, and has no oxidizing tendency.

French investigators, basing the therapeutic value of the vanadium on its hypothetical oxidation power only, were unaware of the main action which really explains most of the phenomena. Jackson believes that the fall in temperature which follows the injection of vanadium is another complicating factor, influencing the respiration as well as the carbon dioxide output to such an unknown extent that no conclusions as to the oxidative properties of the metal in the tissue could be reached.

*Alimentary Canal.*—Vanadium displays a distinct and rather striking action on the gastrointestinal canal. In dogs, cats, horses, and sheep, as well as in man, the primary action of vanadium in acute poisoning is noted in the gastrointestinal canal. The early symptoms are salivation, retching, vomiting, increased peristalsis, free discharge of feces, followed by diarrhea and passage of mucus and blood. Salivation, retching, and vomiting was noted only in cats, dogs, and pigeons. The salivation is probably due to nausea. Jackson was unable to obtain any direct evidence of stimulation of the salivary nervous mechanism. Vomiting appears to be caused by local irritation, and not by central action. A continuous diarrhea in dogs, cats, and pigeons is observed in fatal cases until death. Mice, rats, guinea pigs, rabbits, and sheep exhibit diarrheic stools, only in chronic poisoning. In acute poisoning, the gastrointestinal canal is but little involved. With large and small doses, administered intravenously to horses, a violent increased peristalsis is observed. Jackson noted that vanadium in etherized dogs caused an increased peristalsis, and frequently defecation. The increased peristalsis may last several hours. Thus far we have no explanation for this peculiar action on the alimentary canal. Jackson believes that the action of the metal closely resembles that of veratrine and may be due in part to local irritation, either directly or reflexly.

In chronic poisoning in man and dogs, a diarrhea lasting for days and sometimes weeks is produced, followed at times by a very pronounced and obstinate constipation. In Jackson's opinion there is a pronounced similarity in the action of lead and vanadium, which is evidenced by the increase in blood pressure, urine secretion, etc.

By perfusion experiments on isolated loops of the intestines, Jackson believes that the principal action of the metal on the intestines is due to its effect on the muscular wall. There is also some evidence that a nervous mechanism is also stimulated to activity, causing a



rather prolonged effect on the peristalsis. Epinephrin inhibits the effect of vanadium on the peristaltic movements of the intestine.

*Kidney.*—As both Priestley and Jackson noted vanadium administered daily in small doses undoubtedly exerts a stimulating action on the urinary secretion. Our experiments confirm this phenomenon. Jackson is inclined to believe that this hypersecretion is primarily, if not solely, due to vascular changes, as clearly demonstrated by the alternate contraction and relaxation of the vessels. In Jackson's opinion, a direct stimulation of the renal epithelium either by direct local irritation or by nervous influence appears unlikely, since the urinary secretion in etherized animals is entirely stopped when moderate doses are injected intravenously. This may be explained by the great vasoconstriction of the renal vessels.

In toxic doses albuminuria and cylindruria is constantly observed, a condition which can be readily dissipated by an injection of epinephrin.

*Liver.*—Although no physiological experiments have been made on the liver thus far, we may assume that the vascular changes may influence the metabolism to a considerable extent. The constant presence of vanadium in the liver of animals poisoned by this metal indicates that some important changes may take place.

*Uterus.*—The uterine muscle is entirely unaffected by vanadium in the nonpregnant stages, as well as in late or early stages of gestation. We confirm the findings of Jackson since we have noted no abortions in a great number of animals poisoned by vanadium in the early and late stages of pregnancy. A pregnant sheep which received 250 mg.  $V_2O_5$  did not exhibit any uterine symptoms during the slowly produced vanadium poisoning. The animal which was killed during the acme of the intoxication, did not exhibit any abnormal contractions of the uterine muscle. No vanadium was found either in the placenta or in the fetus.

*Lymph Flow.*—In etherized animals treated with intravenous injections of sodium orthovanadate, Jackson noted that the lymph collected from the thoracic duct showed marked variation, while the head lymph was not appreciably changed. He attributed the increased lymph flow to the increased peristalsis, contraction of the visceral vessels and to the general increased blood pressure.

*Central Peripheral Nervous System.*—The respiratory center exhibits the greatest vulnerability to vanadium since the final respiratory

paralysis and dyspnea are of central origin. With superfatal doses, the consciousness is markedly affected, as depression and somnolence is quickly produced. In the very early stages of the intoxication, when the metal is given in large doses, a marked but short period of excitation is observed. This is seen particularly in rabbits after an intravenous injection. It is impossible to state at present whether this excitation is due to a direct stimulation of the motor and psychic centers or is caused by vascular changes.

According to Jackson the cardio-inhibitory center may be slightly stimulated. Otherwise we have no evidence of direct stimulation of any other part of the central nervous system. A marked stimulation of the sympathetic fibers producing dilation is noted during the entire course of the intoxication. There is no influence on the pupils either by direct application or by subcutaneous or intravenous injection. The peripheral nervous system is not affected by vanadium.

*Temperature.*—Vanadium causes a fall in temperature when injected subcutaneously or intravenously. Priestley observed a drop in temperature of about  $1^{\circ}$  C. following the administration of fatal doses of sodium orthovanadate in guinea pigs. Jackson noted the same phenomenon in his experiments.

In our experiments with rabbits, guinea pigs, mice, rats, and horses, the subcutaneous or intravenous injections of large doses of vanadium caused a lowering of the temperature varying from  $1^{\circ}$  to  $2^{\circ}$  C. A most pronounced fall in temperature was noticed with pigeons. Following the injection of sodium tetravanadate in superfatal doses (2 to 3 mg.  $V_2O_5$  per 100 gm.), in one case a drop in temperature from  $109.2^{\circ}$  F. to  $105.8^{\circ}$  F. was noted, the second case showed a fall in temperature from  $108.4^{\circ}$  F. to  $104.2^{\circ}$  F. in two and one-half hours after injection. The same fall in temperature is observed with much smaller and more readily tolerated doses (.2 to .8 mg.  $V_2O_5$  per 100 gm.) varying from  $1^{\circ}$  to  $5^{\circ}$  F. The minimum temperature was reached two and one-half hours after injection and the normal again attained in one to six hours.

On account of the lack of experimental evidence, it is impossible to state whether this drop in temperature is due to a peripheral or a central disturbance. Jackson thinks that the constriction of the visceral vessels with a corresponding dilation of those of the limbs and skin, causing increased surface heat-losses, is responsible for the

TABLE IV

TABLE IV										
URINE										
Date	Volume	Total Nitrogen	Urea Nitrogen	Uric Acid	Purine Nitrogen	Inorganic Sulphur As SO <sub>3</sub>	Ethierial Sulphur As SO <sub>3</sub>	Neutral Sulphur As SO <sub>3</sub>	Total Phosphor-ous P <sub>2</sub> O <sub>5</sub>	Sodium Chloride.
Apr. 27	1575 gm.	20.02 gm.								
Apr. 28	1500 "	16.80 "	12.90 gm.	.66 gm.	.016 gm.	2.91 gm.	.064 gm.	.126 gm.	3.22 gm.	
Apr. 29	1910 "	17.72 "	13.78 "	.63 "	.019 "	2.70 "	.033 "	.123 "	3.37 "	
Apr. 30	1800 "	16.59 "	15.79 "	.59 "	.019 "	2.82 "	.115 "	.23 "	3.75 "	
May 1	1350 "	15.41 "	13.67 "	.59 "	.019 "	2.81 "	.10 "	.38 "	3.80 "	
May 2	2580 "	17.73 "	15.62 "	.60 "	.016 "	2.81 "	.111 "	.256 "	3.85 "	3.68 gm.
May 3	2800 "	15.85 "	13.94 "	.60 "	.02 "	2.68 "	.107 "	.32 "	3.83 "	4.36 "
May 4	1800 "	15.38 "	14.21 "	.76 "	.02 "	2.64 "	.121 "	.29 "	3.91 "	5.05 "
May 5	2095 "	15.79 "	12.22 "	.53 "	.026 "	2.40 "	.128 "	.42 "	3.97 "	7.08 "
May 6	1960 "	15.84 "	17.29 "	.78 "	.026 "	3.53 "	.122 "	.27 "	3.95 "	4.91 "
May 7	1720 "	16.96 "	15.89 "	.78 "	.020 "	3.01 "	.122 "	.27 "	3.95 "	4.83 "
May 8	1675 "	15.66 "	15.71 "	.78 "	.020 "	2.77 "	.110 "	.46 "	3.94 "	3.43 "
May 9	2500 "	15.35 "	15.81 "	.60 "	.024 "	2.97 "	.112 "	.45 "	3.70 "	4.65 "
May 10	2000 "	13.60 "	15.81 "	.60 "	.024 "	2.97 "	.112 "	.45 "	3.70 "	4.65 "
May 11	2000 "	18.96 "	15.81 "	.60 "	.024 "	2.97 "	.112 "	.45 "	3.70 "	4.65 "
May 12-13	2000 "	16.36 "	15.81 "	.60 "	.024 "	2.97 "	.112 "	.45 "	3.70 "	4.65 "
May 14	1870 "	16.89 "	15.71 "	.60 "	.024 "	2.97 "	.112 "	.45 "	3.70 "	4.65 "
May 15	1795 "	17.02 "	15.81 "	.60 "	.024 "	2.97 "	.112 "	.45 "	3.70 "	4.65 "

temperature changes. After the injection of small doses of vanadium in pigeons, the drop in temperature is probably due to a disturbance of the heat regulating mechanism.

*Influence on Body Weight.*—Animals injected once or twice with tolerated doses of vanadium showed in most cases a rapid increase in body weight. Feeding per os brought about the same result. The continued injection of relatively small doses of vanadium was always accompanied by an increase in body weight. The injection of subfatal doses after several injections with readily tolerated amounts caused a decrease in weight but not below the original weight of the animal. Besides the increase in weight observed by other investigators, French observers also claim that the appetite and strength of the animals are favorably influenced. This claim can not be substantiated by animal experiments alone.

*Metabolism.*—In order to determine the effect of vanadium on the metabolism, a young man in good health, twenty-one years old, was placed on a strictly regulated diet, so that a metabolic equilibrium could be reached as measured by the nitrogen elimination. As soon as a fairly close nitrogen excretion was established, both the urine and feces were collected daily, the quantity of each recorded, and then samples taken for analysis.

On May 10th, the subject received 10 mg.  $V_2O_5$  in the form of sodium

TABLE VII

FECES				
Nitrogen	Phosphorus as $P_2O_5$	Sulphur as $SO_3$	Weight	Total Nitrogen Urine and Feces
2.37 gm.			182 gm.	22.39 gm.
2.18 "			198 "	18.98 "
2.44 "			222 "	20.16 "
1.79 "			242 "	18.38 "
1.83 "			182 "	17.24 "
1.37 "			248 "	19.10 "
3.97 "			397 "	19.83 "
2.09 "	.115 gm.	.172 gm.	170 "	17.47 "
3.34 "	.163 "	.245 "	308 "	19.13 "
2.46 "	.216 "	.166 "	265 "	18.30 "
1.98 "	.200 "	.172 "	192 "	18.94 "
3.32 "	.170 "	.219 "	332 "	18.98 "
1.73 "	.160 "	.144 "	153 "	17.08 "
1.77 "	.216 "	.175 "	165 "	15.38 "
1.90 "	.200 "	.135 "	161 "	20.86 "
2.73 "	.307 "	.149 "	268 "	19.09 "
2.06 "	.258 "	.161 "	231 "	18.95 "
2.10 "	.272 "	.210 "	177 "	19.12 "

tetravanadate, injected intramuscularly. On May 12th and 13th, he received two additional injections of 20 mg.  $V_2O_5$  each. On the evening of May 10th, the final urine was taken at 10 p. m. while usually the twenty-four hour sample was collected from midnight to midnight.

It was impossible to continue the elimination investigation for a longer time because our subject refused to maintain his diet and to collect the daily excretions of urine and feces. It was desirable to continue this experiment to determine if there would be any further changes in the metabolism.

Table VIII gives the changes in the different constituents determined by taking the average of the eliminations for the seven days immediately preceding injection and the average of the four following.

TABLE VIII

URINE				
Constituent	Average before Injection		Average after Injection	Percentage increase or decrease
Total Nitrogen	15.89 gm.		16.64 gm.	+ 4.72%
Urea Nitrogen	14.12 "		15.54 "	+10.05%
Uric Acid	.62 "		.67 "	+ 8%
Purine Nitrogen	.0187 "		.022 "	+12%
Inorganic $SO_3$	2.82 "		2.93 "	+ 3.9%
Ethereal $SO_3$	.111 "		.117 "	+ 5.4%
Neutral $SO_3$	.307 "		.382 "	+24.3%
Phosphorus ( $P_2O_5$ )	3.81 "		.388 "	+ 1.8%
Sodium Chloride	4.77 "		4.72 "	
FECES				
Total Nitrogen	2.39 gm.		2.18 gm.	- 1.7%
Phosphorus ( $P_2O_5$ )	1.86 "		2.61 "	+27%
Total $SO_3$	1.8 "		1.68 "	- 6.6%

In calculating the above results, an average for the figures obtained on May 10th and 11th was used.

The foregoing table clearly shows that the intramuscular injection of 50 mg.  $V_2O_5$  in the form of sodium tetravanadate causes an increased metabolism. The greatest increase is seen in the neutral sulphur (24.3%), the next greatest increase is in the purine nitrogen (12%), then the urea nitrogen (10.05%), uric acid (8%), and total nitrogen (4.72%). There is an increase in all the constituents except sodium chloride which is constant. These results are apparently in accordance with the findings of Berthail who states that "the urine and the oxidation coefficients, in almost all the cases in which the urine was examined from this point of view, were increased."

## DISTRIBUTION OF VANADIUM

Extensive investigations on the distribution of arsenic and antimony show that both are retained in the organism, mainly in the liver. Arsenic is also always found in the spleen, kidney, and muscle. Traces of arsenic are found in the brain, but the bones retain considerable amounts for months and even years, pointing to a substitution of phosphorus by arsenic probably as calcium arsenate.

The close relationship of vanadium to arsenic and antimony would indicate a similar retention in the body. In order to clear up this point, four rabbits and a sheep were injected intravenously with sodium tetravanadate. On account of the difficulty of estimating small quantities of vanadium in the different organs, such as would be found after acute fatal poisoning, only animals injected repeatedly and dying from chronic vanadium poisoning were used. The animals were either etherized or killed by a final fatal dose. The organs were then carefully removed and the vanadium determined.

*Method.*—As large a sample as possible was taken and either dried in the oven at  $110^{\circ}\text{C}$ ., or in the case of liquids, evaporated to dryness on the steam bath. The dried sample was then ignited, the carbonaceous mass moistened with concentrated sulphuric acid, and again ignited to drive out the excess acid. The residue was then extracted with boiling 10% hydrochloric acid, filtered, and the residue again ignited. In case any carbon remained, concentrated, sulphuric acid, containing 10% nitric acid, was repeatedly added in small portions, each followed by ignition until the residue was carbon free. The hydrochloric acid filtrate was then added to the residue and boiled for about 10 minutes, care having been taken to break up all lumps in order to insure a complete extraction. After cooling, the solution was filtered, and the insoluble residue (mainly calcium sulphate) was thoroughly washed. The filtrate was evaporated to as small a volume as practical, but not below 10 c.c. The solution was then diluted with three volumes of alcohol, allowed to stand until the supernatant liquid became clear, filtered, and the residue washed with 70% alcohol. The filtrate and washings were evaporated to 10 c.c. and if more than slightly yellow in color, denoting appreciable quantities of iron, the latter was removed by extraction with ether from the hydrochloric acid solution by Rothe's method. The aqueous solution was then transferred to an evaporating dish, evaporated to dryness, and after

moistening with sulphuric acid, ignited to destroy organic matter, which was invariably present at this point.

With liquid samples such as blood or urine, it was found to be simpler and more expedient to add nitric acid before evaporation, heating cautiously at first, for sometimes, as in the case of blood, a violent reaction takes place. After evaporation to dryness, gentle ignition generally yielded a residue free of carbon. If carbon was left, treatment with sulphuric acid as described before insured a residue free of organic matter. The residue so obtained was then extracted with boiling 10% hydrochloric acid and treated as above.

TABLE IX

DISTRIBUTION OF VANADIUM IN RABBITS				
<i>Rabbit</i>	<i>No. 1</i>	<i>No. 2</i>	<i>No. 3</i>	<i>No. 4</i>
Weight	1539	2260	2280	2190
Vanadium in-	12/19/14— 5 mg.	12/30/14— 3 mg.	12/30/14— 3 mg.	12/30/14
jected as $V_2O_5$	12/28/14— 5 mg.	1/ 2/15— 3 mg.	1/ 2/15— 3 mg.	Received
	12/31/14— 5 mg.	1/ 8/15— 3 mg.	1/ 8/15— 3 mg.	1.2 g. $V_2$
	1/ 2/15— 5 mg.	1/12/15— 3 mg.	1/12/15— 3 mg.	$O_5$ per os
	1/ 3/15— 5 mg.	1/19/15— 3 mg.	1/19/15—15 mg.	in 25 c.c.
	Total —25 mg.	1/23/15— 3 mg.	Total —27 mg.	salt solu-
		1/28/15— 3 mg.		tion by
	Died during the	2/ 6/15— 3 mg.	Etherized two	catheter.
	night.	2/14/15— 3 mg.	hours later.	Died $2\frac{1}{2}$
		2/27/15— 5 mg.		hours
		Total —32 mg.		later.
		Etherized		
		3/2/15.		
	<i>No. 1</i>	<i>No. 2</i>	<i>No. 3</i>	<i>No. 4</i>
Brain	Trace	None	None	
Spinal cord	None	None		
Eye		None		
Lung	0.0006	None		
Liver	0.0029	Faint trace	0.0032	0.0074
Kidney	0.0008	None	0.004	
Suprarenal cap	None	None		
Stomach	0.0008	{ .0015	{ 0.0016	.0127
Stomach contents	Trace			.6564
Small intestine	0.0035			{ .164
Small intestine contents	0.0006			
Large intestine	0.0020			{ .0368
Large intestine contents				
Muscle (leg)	0.0016	None		
Blood (liter)	None	None		
Urine	None	Albumin	0.0032	Heart
Bone marrow	None	None		Lung .0115
Bones		None	None	Kidney
Spleen			None	
Heart			None	

The final residue obtained by one of the foregoing methods was dissolved in 30 c.c. of 30% sulphuric acid, evaporated to fumes of sulphuric acid and the vanadium reduced to vanadyl sulphate with hydrogen peroxide according to Cain's method. The excess of hydrogen peroxide was destroyed by boiling for a few minutes. After cooling, the sulphuric acid solution was diluted to 25 or 30 c.c. with water and titrated with N/40 potassium permanganate. A blank was made at the same time and the reading thus obtained deducted from the reading found. In all cases, the solution titrated was evaporated to fumes of sulphuric acid, reduced with peroxide as before, and again titrated to confirm the first result.

TABLE X

DISTRIBUTION OF VANADIUM IN SHEEP	
Weight	65 lbs.
Vanadium injected intravenously as follows:	
	$V_2O_5$
12/31/14	25 mg.
1/ 8/15	35 mg.
1/20/15	50 mg.
1/30/15	60 mg.
2/12/15	60 mg.
The sheep was chloroformed on the 19th of February, the different organs removed and analyzed for vanadium with the following results:	
Bile	None
Pancreas	None
Peritoneal fluid	Trace
Thymus	None
Spleen	None
Kidney	.0025 mg. $V_2O_5$
Spinal cord	None
Bone marrow	None
Heart	.0015
Brain	.0005
Placenta	None
Lungs	.0041
Muscle	Trace
Blood (liter)	.002
Liver	.004
Stomach and Intestines	.007

WEIGHTS				
Date	Rabbit No. 1	Rabbit No. 2	Rabbit No. 3	Rabbit No. 4
12/19/14	1539 gm.	12/30/14—2260 gm.	12/30/14—2280 gm.	
1/ 3/15	1680 "	1/12/15—2395 "	1/12/15—2485 "	
		1/19/15—2343 "		
		1/23/15—2410 "		
		1/28/15—2337 "		
		2/27/15—2434 "		
		3/ 2/15—2422 "		
Gain	141 gm.	162 gm.	205 gm.	



The intravenous injection of vanadium in repeated doses during several weeks results in the fixation of a part of the vanadium in the liver and kidney, and also in the stomach contents and small intestine probably in course of elimination. In cases where larger doses were given, and the animal died or was etherized shortly after the last injection, vanadium was found also in the lung, heart, blood, muscle tissue, and brain.

The suprarenal capsule, spinal cord, spleen, bones, pancreas, and thymus were free of vanadium. In animals which were accidentally pregnant no vanadium was found in the placenta or fetus. Given by mouth in large doses, considerable amounts of vanadium are found in the heart, lungs, and kidneys and liver, indicating a rapid absorption.

In rabbit No. 2, the presence of a small amount of vanadium in the stomach and intestines with a faint trace in the liver, corroborates the elimination experiment in that no appreciable quantity appears to be retained.

The elimination experiment shows that vanadium in contrast to arsenic and antimony is not cumulative.

#### ELIMINATION OF VANADIUM

From the experiments thus far published, vanadium is eliminated by the gastrointestinal canal. Priestley was unable to detect vanadium in the urine. Jackson stated traces were present. In chronic vanadium poisoning in man, Dutton reported that the nasal and lachrymal secretions may contain traces. Jackson could not confirm these findings, since he could not find any vanadium in the nasal and lachrymal secretions of dogs to which the metal was administered by stomach tubes. The saliva and vomitus were found to be free of vanadium. Jackson believes, and we agree with him, that the vanadium found by Dutton in the nasal and lachrymal secretions is simply due to a mechanical accumulation of vanadium on the mucous membranes. Judged by the lasting effects of vanadium, Jackson considered that a slow elimination took place. To decide this question, a healthy young man, twenty-one years of age, was given daily doses of  $12\frac{1}{2}$  mg.  $V_2O_5$  in the form of sodium tetravanadate per os. All the urine and feces were collected and analyzed for the vanadium, with the results shown in Table XI.

TABLE XI

12½ MG. OF V <sub>2</sub> O <sub>5</sub> TAKEN DAILY BY MOUTH		
<i>Date</i>	<i>Feces</i>	<i>Urine</i>
12/23/14	.0082	.008
12/24/14	.0057	.0004
12/25/14	.0180	.0057
12/26/14	.0229	.0016
12/27/14	.0073	.0008
12/28/14	.0033	.0002
1/2/15	.0064	.0016
1/3/15	.0130	.0016
1/4/15	.0210	.0020
1/5/15	.0074	.0011
1/6/15	.0098	.0012
1/7/15	.0090	.0012
Total recovered	.1321	.0187

In twelve days 0.1508 gm. of V<sub>2</sub>O<sub>5</sub> were recovered, giving a daily average of 12½ mg. the same amount as taken each day, showing that all the vanadium is eliminated. Of this 12.4% is voided in the urine, the balance of 87.6% passing through the feces.

This experiment shows that vanadium is quickly and quantitatively eliminated, mainly through the feces. It confirms the findings of Jackson that no elimination takes place through the saliva, and the lachrymal, nasal and bronchial secretions. Under ideal conditions a given dose of vanadium should be eliminated in twenty-four hours.

#### PRESERVATIVE ACTION

Vanadium, like arsenic, inhibits putrefaction. Binz and Schulz believed that this property was due to oxidation. The putrefactive microorganisms which have pronounced reducing properties cannot thrive in a medium in which oxygen is available. Arsenic or arsenious acid in the presence of an excess of organic matter is slowly transformed into arsenurated hydrogen. The preservative power of arsenic depends on the ratio of the amount present to the quantity of organic matter.

Comparative qualitative experiments with arsenic acid and sodium tetravanadate show that vanadium is less efficient than arsenic as a preservative. When sodium tetravanadate is mixed with organic matter, animal or vegetable, the yellow color of the tetravanadate is changed to green, demonstrating a reduction from pentad to tetrad vanadium. If vanadium is in excess of the organic matter and kept at 37° C., reduction does not go beyond the tetrad valence. When,

however, the organic matter is in excess, the reduction proceeds still further since the green color disappears and the supernatant liquid becomes almost colorless. In this case the putrefaction is no longer inhibited. With vanadium in excess practically all animal organs and tissues, as well as the different excretions, reduce  $V_2O_5$  to  $V_2O_4$  with varying rapidity. When pentad vanadium is injected subcutaneously, reduction to the  $V_2O_4$  takes place, since the subcutaneous tissue shows a green to a blue-green coloration.

The theory of the preservative action of arsenic advanced by Binz and Schulz cannot apply to vanadium. The antiputrefactive power of vanadium may depend to some extent on its oxidizing power, but the fact that it exerts no effect on yeast fermentation up to 5%  $V_2O_5$ , while arsenic inhibits yeast growth, shows that the oxygen cannot be the only factor which inhibits putrefaction. Arsenic as such must exert a toxic effect on yeast while vanadium is atoxic. If this action depended on the oxygen split off, then vanadium should have the same effect as arsenic. It is, therefore, evident that vanadium possesses specific properties upon which its preservative power depends.

#### ACTION ON PROTOPLASM

Whether vanadium enters into combination with any constituent of the protoplasm cannot be stated from the knowledge at our disposal. In a neutral, alkaline, or slightly acid solution, vanadium does not precipitate protein. A solution of egg albumen containing 1%  $V_2O_5$  in the form of sodium tetravanadate requires 1.87 c.c. normal hydrochloric acid per 100 c.c. before precipitation takes place. All living protoplasm causes a reduction of vanadium to its lower oxides. Hemoglobin in vitro is converted to methemoglobin by a 1% solution of  $V_2O_5$  in the form of ammonium metavanadate while a similar concentration of sodium hexavanadate causes no change.

#### PATHOLOGY

Priestley gave but a macroscopic description of the pathological changes found in animals poisoned by vanadium. From his observations, it appears that vanadium given as sodium orthovanadate per os, subcutaneously or intravenously in superfatal doses, produces a more or less pronounced hyperemia combined with multiple hemorrhages in the mucous membranes of the stomach, small intestines and, to a

lesser degree, in the large intestines and rectum. Free blood was sometimes found in the contents of the small intestines.

The heart in the majority of cases showed a dilation of the right and a contraction of the left ventricle. In two instances the lung showed congestion and multiple subpleural hemorrhages, as far as can be judged from the description given. The kidney and liver were found to be either normal or slightly congested. No microscopic examination of the organs was made. He found that the coagulability and the optical properties of the blood were not altered.

The influence of the vanadium upon the circulating red cells was mainly studied clinically, rather than experimentally, in animals. A number of French clinicians reported that the continued use of small doses of vanadium will cause a numerical increase of the erythrocytes and also a rise in hemoglobin. It is generally accepted that the action of vanadium upon the red cells is similar to that of arsenic, in spite of the difference in the pharmacological action of these two metals.

Jackson reported an increase in the red cells in some animals, and also observed nucleated red cells. The appearance of the latter is obscure. No change in the microscopical aspect of the red cells, or marked changes of the leucocyte picture were observed. The clotting of the blood and the spectroscopic properties showed no change. Jackson mentioned in acute vanadium poisoning that the left heart and coronary arteries were contracted to their utmost limit, while the right heart was normal.

Dutton reported that the principal lesions of vanadium poisoning in man were found in the lungs, kidneys, and gastrointestinal tract. The lungs were greatly congested and showed a marked destruction of the alveolar epithelium. The kidney lesions are described as a hemorrhagic nephritis. The gastrointestinal canal showed evidences of irritation and inflammation. A detailed macroscopic or microscopic description was not given.

Dowdeswell found that cats and dogs injected either subcutaneously or fed per os with ammonium vanadate (probably metavanadate) showed a more or less marked fatty degeneration of the liver. Guinea pigs and rabbits under the same treatment showed no fatty degeneration. In carnivora besides fatty degeneration he found the well defined lobules entirely effaced. The hepatic cells become coarsely granular and their nuclei and nucleoli became pale and disappeared. At the same time the boundaries of the cell were rendered indistinct

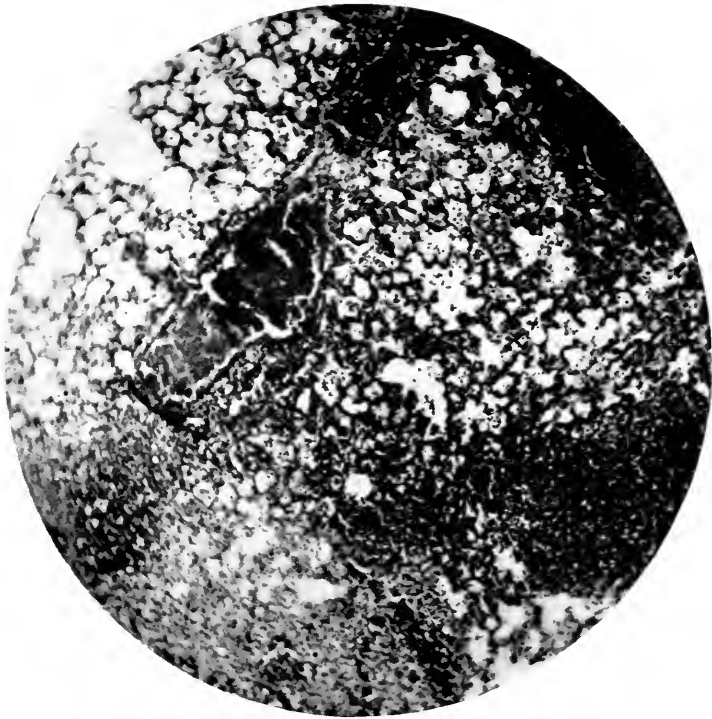


Fig. 5.—Lung showing localized leucocyte infiltration and venous congestion. Guinea pig poisoned with colloidal vanadium pentoxide. Leitz objective 3. ocular 2.



and appeared as a homogeneous fused mass. The intralobular vessels were greatly congested and the intracellular bile pigment was greatly diminished. The fatty degeneration commenced in the periphery of the cells, and progressed to the center of the acini, the hepatic cells around the hepatic vein were usually unchanged. In rodents these changes were not so well defined. He also mentioned that the mucous membrane of the intestinal canal was generally congested, beyond this, the pathological changes in the other organs were not well marked.

#### (a) ACUTE POISONING

In acute vanadium poisoning, if the animal dies in a few minutes after the intravenous injection of a soluble vanadium salt, a marked dilation of the blood vessels results, particularly the venous vessels. The lungs are either normal or slightly hyperemic, sometimes a few small punctate subpleural hemorrhages are seen. The left ventricle and auricle of the heart, as well as the coronary vessels, are frequently found greatly contracted. The right ventricle and auricle on the other hand, is rather soft and distended with blood. The liver, kidney, and spleen are more or less hyperemic. The pancreas, suprarenal capsule, and genital organs are of normal appearance. The pia arachnoidea of the brain and spinal cord is usually injected, and the blood vessels of the gray and white substance are congested. The microscopic changes are in agreement with the macroscopic findings, and consist of a marked dilation of the venous vessels, and sometimes also of minute hemorrhages. There is no appreciable change in the cells of the parenchyma. The intense contraction of the arterial vessels is most striking. The ganglion cells of the brain and of the medulla oblongata show a slight diminution of the tigroid substance.

#### (b) SUBACUTE AND CHRONIC POISONING

Constant and typical changes are found in subacute and chronic vanadium poisoning. The vascular changes are common in all animals. These consist chiefly in congestion of the venous system and typical lesions in the lungs and kidneys.

*Lungs.*—The lungs are usually of a semisolid consistency, and do not collapse on opening the pleural cavity. The surface is of a mottled grayish red color. The grayish fluffy areas protrude slightly above the reddish. The latter are of a semisolid consistency, and in lobular arrangement, and are most numerous in the posterior part of the lower

lobes. Sometimes deep red round nodules of a firm consistency and of various sizes are seen, slightly protruding above the lung surface (horse and sheep). On section, the lungs are enormously edematous, and more or less hyperemic. By applying pressure, a frothy bloody fluid escapes. The air content is diminished. In cases of prolonged death, the lower lobes are sometimes completely atelectatic. The cut surface shows numerous grayish red, slightly sunken areas of irregular shape and size, apparently air free. The remainder of the parenchyma is of a grayish-white color and contains air. The firm nodules mentioned above are triangular in shape, the base toward the lung surface. They are of a dark red color and atelectatic. Some of the larger pulmonary veins are thrombosed and the pulmonary arteries are unchanged. The bronchi may or may not contain a bloody mucus. The mucous membrane is considerably swollen. The mucous membrane of the large bronchi is deep red in color and may be covered with a thin mucus.

The enormous engorgement of the capillary vessels is the most striking microscopic finding. The congested capillaries protrude in the form of small buds into the air vesicles. The capillary arteries are often ruptured, filling the air vesicles with blood. The blood-filled air vesicles may fuse to a homogeneous red mass. These areas may contain a more or less granular brownish pigment, while a few of the air vesicles are filled with a serous exudate containing very little fibrin. Where the parenchyma is free of hemorrhages and cellular infiltrations, a rarefaction of the stroma takes place uniting several of the air vesicles (compensatory emphysema). The stroma is compressed. The alveolar epithelium is swollen and many air vesicles are filled with desquamated epithelial cells. The pulmonary veins are greatly congested, partially ruptured, and most of them are densely surrounded by polynuclear leucocytes. The leucocyte infiltration may either surround the entire lumen, or form a broad roundish irregular infiltrated area, or a circumscribed leucocyte infiltration, merely attached to the vessel wall, may follow the course of the pulmonary vein.\* Where the leucocyte infiltration appears, the air vesicles are entirely filled with leucocytes, remnants of alveolar epithelium and stroma cells. The capillaries are sometimes preserved but in the very dense infiltrated areas they are no longer evident. The infiltrated areas are chiefly composed of polynuclear leucocytes and a

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\*No leucocytic infiltration occurs in the lungs of frogs.



few mononuclear cells. The presence of fibrin could not be demonstrated by Weigert's method. In the center of the infiltrated areas, regressive changes are frequently noted. The leucocytes show all stages of degeneration, vacuolation of the protoplasm, nuclear disintegration, and complete necrosis. Many of the pulmonary veins are thrombosed either in whole or in part. The pulmonary arteries are unchanged. Their lumen appears to be more contracted than normal. Leucocyte infiltrations are also seen around the larger bronchi. The mucous membrane of the bronchi is swollen and its lumen may contain erythrocytes, polynuclear leucocytes, and granular masses.

*Kidneys.*—In subacute poisoning, the kidneys are slightly enlarged, the capsule stretched but readily removed. The surface is smooth gray-red to dirty gray-red in color. On section the cortex and medullary substance are congested. In chronic poisoning, the kidney may be considerably enlarged, the surface smooth and the surficial veins distinctly visible. The tissue is of a faded gray yellow color. On section the cortex is enlarged and gray yellow in color. The normal striations are effaced, and the cut surface shows congestion. The pyramids are somewhat pale red, with distinct striations. The pelvis is unchanged.

Microscopically the kidney\* in acute poisoning may show a pronounced hyperemia, with perhaps a less distinctly stained epithelium of the convoluted tubules. In mammals and birds, in subacute or chronic poisoning, the characteristic changes are either a partial or a complete necrosis of the epithelium of the proximal and medial part of the convoluted tubules. The glomeruli are hyperemic. Henle's loops, "die Schalt and Zwischenstücke," as well as the collecting tubules, are unaffected. In very severe poisoning (colloidal vanadium pentoxide) the distal part of the convoluted tubules may also show necrosis of the epithelium, and signs of cellular degeneration may be seen in the glomeruli and the proximal parts of Henle's loops consisting in a vacuolation of the protoplasm and less distinctly stained nuclei. An exudate may occur in Bowman's capsule, but hemorrhages are rarely observed. In batrachians, necrosis of the epithelium of the glomeruli is the only change, while the remainder of the secretory apparatus is unaffected.

The intensity of the necrosis varies with the individual as well as

\*In regard to the names of the different parts of the convoluted tubules, the nomenclature of Peter was followed. The localization of the lesions was established by simultaneous injections of carmine.

with the animal species. The horse kidney is the most sensitive to vanadium since 1.1 mg. of  $V_2O_5$  in the form of sodium tetravanadate per kilogram weight will produce a distinct necrosis of the epithelium of the proximal and medial parts of the convoluted tubules.\*\* The necrosis of the epithelium in the early stages of the poisoning is preceded by the secretion of a drop-like lumpy mass expelled upon the surface of the epithelium. In cases of complete necrosis, the tubules are filled with a homogeneous drop-like lumpy material or with a stringy coagulated mass, packed with necrotic protoplasmic substances. Sometimes a few red cells are found in the necrotic masses. In Henle's loops, in the descending as well as the ascending parts, hemorrhages and well formed cylinders occur. Cylinders are also found in the "Schalt stücken" and collecting tubes. The venous vessels are greatly dilated and may or may not show a perivascular infiltration. There is no change in the arteries. Albumin, hyalin, and granular casts are found in the urine. After moderate vanadium poisoning, the necrotic renal epithelium is completely regenerated without interstitial changes.

*Gastrointestinal Canal.*—The gastrointestinal canal shows a hemorrhagic gastroenteritis. Free blood, leucocytes, and desquamated epithelial cells may be found in the intestinal contents. The lesions vary greatly in the different animal species. In mice, rats, guinea pigs, and rabbits, the gastrointestinal lesions are not very pronounced. The most intense gastroenteritis is found in pigeons, chickens, and horses. In pigeons the process extends throughout the intestinal canal, while in horses it is almost entirely localized in the colon. The venous vessels throughout the entire wall of the gastrointestinal canal are markedly dilated when examined microscopically. The vessels of the mucous membrane are intensely injected and partially ruptured, emptying their blood into the lumen of the intestines or into the glandular tissue. The entire mucous membrane is sometimes intensely infiltrated with leucocytes, especially with polynuclear eosinophiles. Superficial necrosis of the mucous membrane is common.

*Liver.*—The liver may be enlarged and of a cloudy grayish red color and of a soft and friable consistency. On section, it is more or less hyperemic, the acinus picture is indistinct or entirely effaced. The hepatic veins are dilated. The gall bladder is usually distended and contains a thin green bile.

Microscopically a marked venous congestion with perivascular in-

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\*\*Vanadium affects the same parts of the convoluted tubules as chromium.

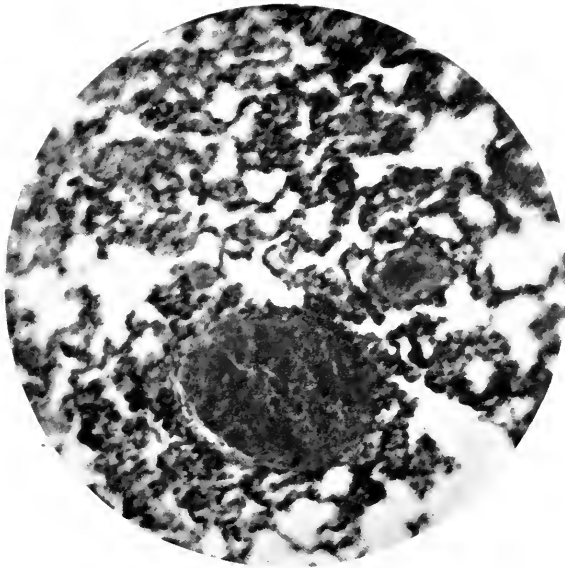


Fig. 6.—Lung showing engorgement of the capillaries and pulmonary veins. Guinea pig poisoned with colloidal vanadium pentoxide. Leitz objective 4, ocular 2.

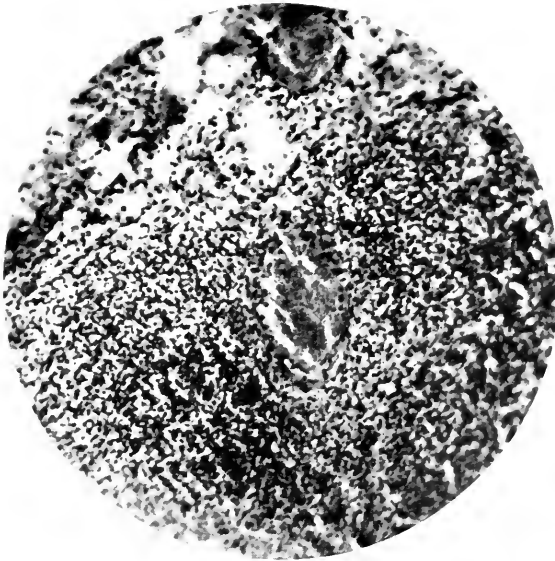


Fig. 7.—Lung showing marked perivascular infiltration of pulmonary vein. Guinea pig poisoned with colloidal vanadium pentoxide. Leitz objective 4, ocular 2.



filtration of the hepatic veins and circumscribed hemorrhages are noted. The liver may show the most extensive hepatitis with a diffuse infiltration of polynuclear leucocytes combined with necrosis of the cells, depending upon the intensity of the poisoning. Fatty degeneration to a marked extent was noted only when colloidal vanadium pentoxide was injected. The bile capillaries and arteries are unchanged. In severe poisoning, bile pigment will be found in the urine.

*Heart.*—In chronic poisoning, the heart is usually of a flabby consistency in both ventricles. The myocardium shows a marked dilation of the venous vessels while the arteries are greatly contracted. Sometimes thrombosis of the veins occurs. The striation of the muscle fibers is perhaps less distinct than normal. The nuclei of the muscle fibers in cases of intense intoxication show pycnosis, but otherwise no appreciable regressive changes are noted.

*Spleen.*—The spleen is slightly enlarged, and of a deep bluish red color. On section it shows marked congestion with the pulp protruding. Microscopically the pulp shows an intense hemorrhagic infiltration. The follicles are well preserved. The veins of the pulp are greatly congested and are sometimes ruptured. The arteries are contracted. The hemorrhagic infiltrated pulp shows considerable brownish granular pigment. Sometimes a diffuse infiltration of the pulp polynuclear neutrophiles occurs. The capsule may be thickened and infiltrated with leucocytes.

*Lymph Glands.*—The bronchial and abdominal lymph glands may be slightly enlarged and hyperemic. On microscopic examination, venous congestion, edema of the peripheral lymph sinuses, hemorrhages in and around the lymph follicles, and a more or less pronounced infiltration with polynuclear neutrophiles or eosinophiles is evident.

*Suprarenal Capsule.*—The suprarenal capsule is usually hyperemic. Microscopically a marked venous congestion with a slight perivascular infiltration, small hemorrhages in the cortical and medullary substance, and a greater or less infiltration with polynuclear leucocytes may be noted. The chrome reaction is perhaps less distinct than normal.

*Central Nervous System.*—The central nervous system, including the pia arachnoidea, shows a pronounced congestion. The venous vessels of the pia arachnoidea, as well as of the gray and white matter, show a more or less pronounced perivascular infiltration. The majority of the pyramidal cells of the cortex show a less distinctly

stained nucleus and a diminution of the tigroid substance. The neuroglia appear to be unchanged by the common staining methods. The most pronounced changes are found in the posterior parts of the medulla oblongata. The ganglion cells of the respiratory center are disarranged, and show all stages of disintegration, disappearance of the tigroid, vacuolar degeneration of the protoplasm, chromatolysis of the nuclei, and complete necrosis. The surrounding neuroglia show rarefaction.

*Bone Marrow.*—In acute and subacute poisoning, the bone marrow shows no change in its cellular character. In chronic intoxication, an increase of the neutrophile myelocytes and a decrease of the lymphoid elements is apparent. No increase in the nucleated red cells was observed. The capillary vessels are markedly congested. Hemorrhages may occur.

*Blood.*—The following vanadium salts, colloidal vanadium pentoxide, sodium tetravanadate, sodium hexavanadate, ammonium vanado-arsenate and ammonium vanadi-arsenate, were injected intravenously into rabbits to determine their influence on the circulating blood cells. The results of the blood examinations are given in Table XII.

The simple vanadium salts have practically no influence on the red cells. The white cells are slightly increased, while the hemoglobin is slightly diminished when tolerated doses are injected. No degenerative changes in the red cells were noted. Occasionally a few nucleated red cells were seen but whether these were due to the vanadium is problematical, since nucleated red cells are frequently found in the blood of normal rabbits.

After the injection of colloidal vanadium pentoxide, there was a relative increase in the pseudoeosinophiles, and a decrease in the lymphocytes. The remainder of the leucocytes with the exception of the basophiles, which were slightly increased, was not changed. After the injection of sodium tetravanadate for an extended period of time, no change in the leucocyte picture was noted. On the other hand sodium hexavanadate causes a marked relative increase in the pseudoeosinophiles. On the second day after injection, an unusually high number of basophiles were found.

Ammonium vanado-arsenate exhibits no marked influence either on the number of the red and white cells or on the hemoglobin content. Ammonium vanadi-arsenate on the other hand, increases the red cells

TABLE XII  
INFLUENCE OF VANADIUM ON THE BLOOD OF RABBITS

Colloidal Vanadium	Sodium Tetra vanadate	Sodium Hexavanadate	Ammonium Vanado-arsenate	Ammonium Vanadi-arsenate
Rabbit 2060 gm. received from Feb. 29, to Mar. 4, 1916, 11.2 mg. $V_2O_5$ or 2.8 mg. daily intravenously.	Rabbit 1950 gm. received from Jan. 25 to Feb. 29, 1916, 60 mg. $V_2O_5$ intravenously, average dose 5 mg.	Rabbit 1830 gm. received on May 18, 1916, 45.75 mg. $V_2O_5$ .	Rabbit 2295 gm. received on May 25, 1916, 20mg.	Rabbit 2390 gm. received May 25, 1916, 14.34 mg.
	<i>Blood Count Before Injection</i>			
Red Cells	Feb. 29, 1916. 6,300,000	Jan. 25, 1916. 6,300,000	May 25, 1916. 5,700,000	May 25, 1916. 6,000,000
White Cells	9,800	11,000	14,000	12,000
Hemoglobin	14.04 gm.	12.56 gm.	11.04 gm.	11.96 gm.
Pseudocoinophiles	53.5%	60.70%	23%	50%
Eosinophiles			1%	9%
Small Lymphocytes	44.5%	36.30%	68%	38%
Medium Lymphocytes	2%	2.80%	8%	3%
Basophiles				
	<i>Blood Count After Injection</i>			
Red Cells	Mar. 4, 1916. 6,500,000	Mar. 2, 1916. 6,500,000	May 26, 1916. 5,800,000	May 26, 1916. 6,000,000
White Cells	10,750	12,500	15,000	14,000
Hemoglobin	13.16 gm.	10.16 gm.	11.04 gm.	12.24 gm.
Pseudocoinophiles	64.5%	59.5%	50%	57%
Eosinophiles			1.0%	3%
Small Lymphocytes	30%	20.20%	39%	35%
Medium Lymphocytes	1%	.42%	10%	5%
Basophiles	1%	4.27%		
Monocytes				
	<i>Blood Count After Injection</i>			
Red Cells	Mar. 6, 1916. 6,300,000	Mar. 20, 1916. 5,800,000	May 27, 1916. 5,900,000	May 27, 1916. 6,500,000
White Cells	12,000	13,500	13,500	14,200
Hemoglobin	12.56 gm.	10.48 gm.	11.64 gm.	12.56 gm.
Pseudocoinophiles		38%	48.33%	41.5%
Eosinophiles		1%	0.38%	7.5%
Small Lymphocytes		47%	46.46%	43.5%
Medium Lymphocytes				
Basophiles				
	<i>Blood Count After Injection</i>			
Red Cells	Mar. 17, 1916. 6,500,000			
White Cells	11,500			
Hemoglobin	12.56 gm.			
Pseudocoinophiles	62.80%			
Eosinophiles	93%			
Small Lymphocytes	18.60%			
Medium Lymphocytes	14.40%			
Basophiles	3.20%			

and hemoglobin to an appreciable extent and causes a slight leucocytosis. The relative leucocyte count in both cases shows a decrease in the pseudocoinophiles and an increase in the lymphocytes. The remainder of the leucocytes are not changed.

In order to determine the influence of vanadium on the erythrocytes, leucocytes and hemoglobin in man, a case of myeloid leukemia was injected intravenously with sodium tetravanadate. In six days, the patient received 65 mg.  $V_2O_5$  in doses of 10 to 20 mg. The results of the blood examination, as well as a record of the blood pressure and temperature is given in Table XIII.

TABLE XIII

RESULTS OF BLOOD EXAMINATION									
Date	Red Cells	White Cells	Hemoglobin	Temperature	Blood Pressure Systolic	Blood Pressure Diastolic	Pulse Pressure	Mg. $V_2O_5$	
Mar. 26, 1916.	2,720,000	680,000	9.56 gm.	100.2° F.	105	75	30	10 mg.	
Mar. 27, 1916.	2,650,000	700,000	8.96 "	99.4° F.	115	85	30	10 mg.	
Mar. 28, 1916.	2,550,000	671,000	8.96 "		110	70	40		
Mar. 29, 1916.	2,440,000	645,000	9.24 "	99.6° F.	105	75	30	10 mg.	
Mar. 30, 1916.	2,440,000	650,000	8.96 "	98.6° F.	115	85	30	15 mg.	
Mar. 31, 1916.	2,800,000	676,000	9.56 "	97.2° F.	115	85	30		
Apr. 1, 1916.	2,380,000	680,000	8.96 "		110	80	30	20 mg.	
Apr. 2, 1916.	2,400,000	660,000	8.96 "	100° F.	115	85	30		
Apr. 3, 1916.	2,500,000	650,000	8.96 "	98.6° F.	110	85	25		

The foregoing table demonstrates that vanadium in the form of sodium tetravanadate has no influence on the red cells, white cells, or hemoglobin. The blood pressure appears to be slightly increased and the temperature lowered.

## SUMMARY

The general distribution of vanadium in nature, if only in the merest traces, leaves no doubt but that this element in a certain geological epoch of our planet must have been of far greater importance in plant life than today. It occurs in plant ashes although in extremely small quantities. On the other hand, the ash of the South American coals runs comparatively high in vanadium. In some coals with a total ash ranging from .63% to 1.2% the percentage of  $V_2O_5$





Fig. 8.—Liver showing necrosis of hepatic cells and congestion of hepatic veins. Guinea pig poisoned with colloidal vanadium pentoxide. Leitz objective 3, ocular 2.

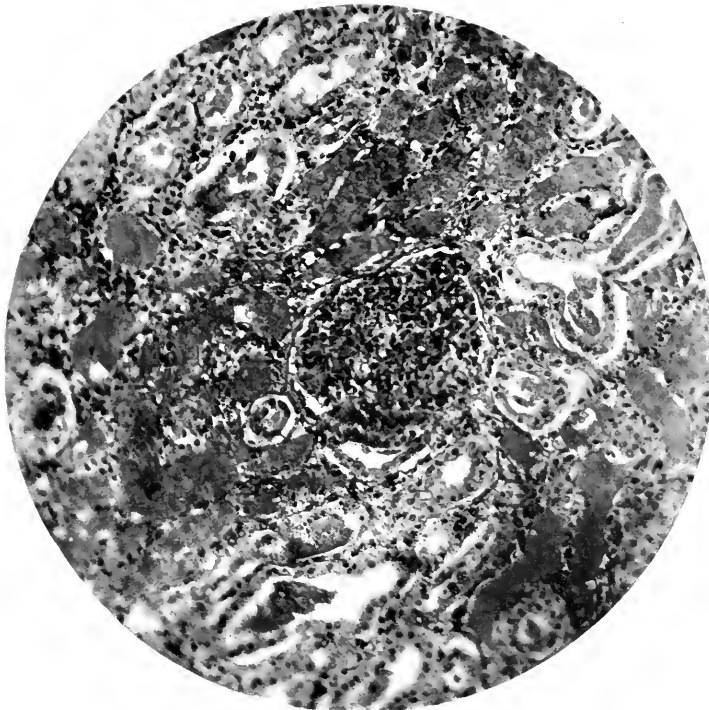


Fig. 9.—Kidney showing necrosis of the first and second part of the convoluted tubules—cylinder formation and hyperemia of the glomerulus. Horse intravenously poisoned by sodium tetravanadate. Leitz objective 4, ocular 2.



in the ash may run as high as 38%. Analyses are not available to determine whether vanadium substituted phosphorus in whole or part. It is, therefore, rather unexpected that vanadium exerts a harmful action on present plant life. Whether the traces of vanadium found in the ashes of a number of plants are of physiological importance to the plant life, or merely accidentally stored up, is open to question.

The occurrence of considerable amounts of vanadium in the acid-reacting blood of lower maritime animals (*Ascidia*, *Phallusia mamillata*) is of the greatest physiological interest. Undoubtedly, the vanadium chromogen in an acid medium plays the role of an oxygen carrier like the hemoglobin in the higher animals. Vanadium, one of the most toxic elements for higher animals, in the case of certain maritime animals is a necessity for life.

Chemically, vanadium is very closely related to nitrogen, phosphorus, arsenic, antimony, and bismuth. In its oxides it follows nitrogen very closely, and has a valency from two to five. The lower oxides have a purely metallic character; with the increase in valence, acid properties are acquired. The acids derived from the pentoxide of vanadium resemble those of phosphorous and arsenic. Vanadium forms an innumerable number of salts due to its tendency to form more complex aggregations than phosphorus or arsenic. The most stable salts are derived from the tetroxide and pentoxide, or from both.

Vanadium, in neutral or slightly acid solution, does not precipitate protein bodies. It inhibits putrefaction to a certain extent, and, at the same time, is reduced to a lower oxide.

The toxicity of the vanadic acids appears to depend upon the number of hydroxyls attached to a vanadium atom and also upon the presence of the  $\text{VO}_2$  complex. Colloidal vanadium pentoxide and ammonium metavanadate are the most toxic salts, while vanadyl sulphate and sodium hexavanadate are the least toxic of those with which we have experimented. Mice and rats are the most resistant to vanadium, rabbits and horses the most sensitive.

Vanadium poisoning is dominated by two groups of symptoms which may develop simultaneously. One is the result of depression, and, in severe intoxication, acute paralysis of the respiratory center; the other is due to pulmonary, kidney and gastrointestinal lesions. The former causes unconsciousness, coma, failure of respiration and

circulation, and paralysis of the respiratory and vasomotor centers. The extreme fall of temperature in acute poisoning may also be due to a paralysis of the heat-controlling central mechanism. The lesions in the lungs cause increased respiration and dyspnea. The kidney lesions cause albuminuria and cylindruria and, in severe cases, anuria. The gastrointestinal lesions cause vomiting, increased peristalsis and hemorrhagic diarrhea. The pulmonary and gastrointestinal disturbances and the disturbance of the circulation appear to be closely related, since they may develop at the same time, with a drop in blood pressure and a small weak pulse. The circulatory failure is due to a weakening of the heart muscle and a complete paralysis of the contractile elements of the pulmonary capillaries and also of the capillaries of the portal system so that the blood stagnates and accumulates in them and their veins.

The chief action of vanadium is exerted on the vascular system. An intense peripheral constriction of the vessels of the lung, spleen, kidneys, and intestines results. The peripheral vessels (cutaneous and muscular) are dilated by visceral displacement of the blood in the intact animal. From perfusion experiments on the limb, it appears that vanadium has also a slight action on the peripheral vessels, since the volume of the limb is decreased. The vasoconstriction is purely local in character and is produced within the organs. The vasoconstriction produced by vanadium in the intact animal and the decrease produced by epinephrin may be considered as pointing toward a nervous as well as a muscular action by vanadium. The stimulating effect of vanadium upon the myoneural junctions in certain forms of smooth muscle seems to be almost specific for this metal, since no other metallic substance or vegetable poison has a similar action (Jackson).

In *lumbricus terrestris* vanadium seems to have a direct effect upon the muscular apparatus, first stimulating, then later paralyzing it. There is practically no effect on the mammalian heart, while the batrachian and chelonian heart appears to be more directly affected. The vagus endings are not influenced. The rise in the general blood pressure is not due to a stimulation of the medullary vasoconstrictor center, but to the constriction of the peripheral vessels. Repeated intravenous injections cause a weakening and paralysis of the vasoconstrictor center, and perhaps have a direct depressing action on the heart. The respiration is at first stimulated, but with diminished depths, followed by a gradual slowing and final dyspnea until death

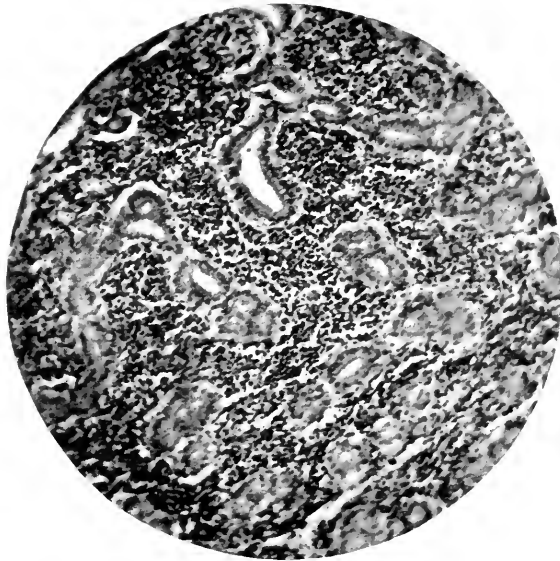


Fig. 10.—Small intestine showing intense hemorrhagic inflammation. Pigeon poisoned with sodium tetravanadate. Leitz objective 4, ocular 2.

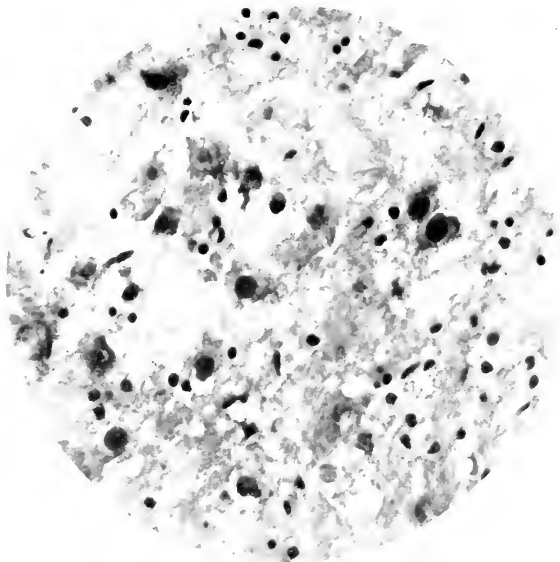


Fig. 11.—Medulla oblongata respiratory center, showing necrosis and neurobiasts of the ganglion cells and rarefaction of neuroglia. Rat poisoned with colloidal vanadium pentoxide. Leitz objective 6, ocular 2.



ensues. Vanadium also causes constriction of the bronchi. The metal cannot be regarded as an oxygen carrier since pervanadic acid cannot be formed in the body. The blood of animals poisoned by vanadium shows no change in its spectroscopic properties and time of coagulation.

The lymph flow and the urine secretion are increased. The influence of vanadium on the liver has not been investigated, but the increase in the urea output points to metabolic changes in this organ. The uterine muscle is not influenced. The action on the gastrointestinal canal is rather striking; salivation, retching, vomiting, an increased peristalsis and diarrhea are observed. In chronic poisoning, diarrhea followed by a pronounced obstinate constipation, as in lead poisoning, is noted. The proteolytic activity of pepsin, as well as the amylolytic activity of pancreatin, is absolutely inhibited in concentrations of 0.2%  $V_2O_5$ . The central nervous system is affected only by fatal doses, causing depression and somnolence. The peripheral nervous system is not affected. The sympathetic fibers are stimulated. The body weight is increased when vanadium is given in tolerated doses for a long period. The metal is temporarily fixed in the liver, kidneys, stomach, and intestines, and is finally entirely eliminated, mainly in the feces. The metabolism is accelerated, causing an increased output of neutral sulphur, purine nitrogen, urea nitrogen, and uric acid. The temperature of normal animals is lowered by vanadium; this is most pronounced in pigeons. Vanadium has slight bactericidal properties, but a pronounced protozoicidal action, particularly toward *spirochete pallida*.

Typical pathological changes are found in subacute and chronic poisoning. The ganglion cells of the respiratory center, the pulmonary veins and capillaries, the epithelial cells of the convoluted tubules of the kidney, and the capillaries of the intestines are the most sensitive to vanadium. Hyperemia, hemorrhages, perivascular infiltration, edema, diffuse or localized leucocyte infiltration in almost all the organs, and parenchymatous cell necrosis are of usual occurrence. The lung changes, which were entirely overlooked by early investigators, are the most characteristic signs since they were found in all cases of vanadium poisoning. Hemorrhages, edema, thrombosis and perivascular infiltration of the pulmonary veins, and multiple localized leucocyte infiltration, giving the picture of a bronchial pneumonia are always found in all mammals poisoned by vanadium. The

changes in the kidney are less constant. Some animals show no signs of necrosis of the epithelial cells of the convoluted tubules, in spite of the most intense vanadium intoxication. Necrosis of the first and second part of the convoluted tubules is typical in all cases of moderate vanadium poisoning. The third part is affected only in the most severe cases of poisoning. As a rule the glomeruli, Henle's loops, and the collecting tubules are unchanged. Cylinders may be found in the latter structures. Fatty degeneration, when present, is confined to the same structures as the epithelial necrosis. The horse kidney is most sensitive to vanadium. Necrosis of the epithelial cells of the first and second parts of the convoluted tubules may be caused by one milligram of  $V_2O_5$  per kilogram of animal, while no changes are caused in other organs. Albuminuria and cylindruria are found in all cases of vanadium intoxication. The gastrointestinal canal is less affected than any other organ, and pronounced changes are found only in pigeons and horses. An intense hemorrhagic enteritis of the entire intestinal canal is caused in pigeons and chickens when superfatal doses are administered. In horses, on the other hand, the hemorrhagic inflammation is localized in the colon. In intense intoxication, the liver shows fatty degeneration, necrosis, and diffuse inflammation. The spleen and lymph glands show congestion, hemorrhages and leucocyte infiltration. The principal lesions of the central nervous system are found in the respiratory center, showing a destruction of the ganglion cells. The changes in the remaining organs are mainly hemorrhage, edema, and leucocyte infiltration. Vanadium in tolerated doses has practically no influence on the circulating blood cells. The red cells remain unchanged in number and suffer no degeneration. However, in chronic intoxication, the red cells appear to be directly affected by the metal since the spleen contains a considerable amount of blood pigment. The bone marrow occasionally shows an increase in the neutrophile myelocytes, while the lymphoid elements are decreased. The leucocytes, especially the neutrophiles, are slightly increased.

The pathological changes characterize vanadium as a neurotoxic and a hemorrhagic-endotheliotoxic poison with a hepatotoxic, nephrotoxic, and probably leucocytaetic and hemotoxic component. The neurotoxic action is vitiated by the necrobiosis and necrosis of the ganglion cells of the respiratory center. The hemorrhagic-endotheliotoxic action causes serous transudation and hemorrhages (per diapedesin and



per rhexin) mainly into the lung vesicles and intestines, with desquamation of the epithelial lining of these organs. The mucous membranes of the bronchi and the intestinal canal are directly injured as a result of the stasis. A direct action by vanadium could not be demonstrated. The superficial necrosis which is sometimes seen in the mucous membrane of the colon is not due to the vanadium excreted through it, but to bacterial causation. The hepatotoxic and nephrotoxic action demonstrates a selective action of the metal for the hepatic cells and secretory cells of the kidneys. The pathological changes show that the increased activity of these cells is, therefore, not only due to vascular changes, but also to the direct stimulation of the vanadium resulting in an increased urea formation and an increased urine secretion. The leucocytaetic action is shown by the intense leucocyte infiltration in the lung, and to a lesser degree in the remainder of the organs. The action on the leucocytes is probably a direct chemotactic effect on these cells. The presence of a pigment in the spleen giving the iron reaction (hemosiderin) in animals dying of chronic vanadium poisoning is undoubtedly a sign of the hemotoxic action of the metal.

#### THERAPEUTIC INDICATIONS

A critical review of the literature on the therapeutic use of vanadium clearly demonstrates that the previous therapeutic utilization of this drug was haphazard, and not sufficiently based on scientific data. Heretofore, the metavanadates, the most toxic of the vanadium salts, were mainly used in actual practice. The French authors attributed the therapeutic properties of vanadium to its oxidizing power, chiefly as a carrier of oxygen. Since pervanadic acid cannot be formed in the body, and since pentad vanadium on injection is immediately reduced to the tetrad oxide, this theory is flatly contradicted by fact. The physiological action of vanadium must be due to its inherent properties. The clinical observations of the French investigators show that sodium metavanadate given in small repeated doses, exerts a beneficial influence on the nutrition, increases the appetite and body weight, and stimulates the protein metabolism and diuresis. No specific action of the drug was noted. Solutions of the pentoxide were also used in surgery, gynecology, and ophthalmology. A stimulating effect on the granulation tissue, a lessening of suppuration, and a promotion of healing was observed.

Jackson suggested that the vasoconstrictor action of vanadium might

be used in the treatment of pathological conditions of the abdominal organs, in toning up the vessels of the splanchnic area and increasing peristalsis, and by vascular changes in the kidney, increasing diuresis. He stated that the vasoconstrictor action on the vessels of the lungs could not be utilized therapeutically since the susceptibility of these structures to the action of vanadium is much less than that of the vessels of the abdominal organs and, therefore, would require excessive doses of vanadium which could not be tolerated medicinally. No reports are available as to the value of vanadium in these conditions.

The following suggestions for the therapeutic use of vanadium are based on our experimental investigations and clinical experience.

#### DOSAGE AND TOXICITY OF VANADIUM FOR MAN

The first salt employed in our therapeutic work was sodium tetravanadate, of which the safe dose intravenously is 10 mg. as  $V_2O_5$ . Doses of 20 mg.  $V_2O_5$ , intravenously injected, produce acute intoxications in some individuals, as described in an earlier part of this paper. 30 mg.  $V_2O_5$  as tetravanadate, intravenously injected, undoubtedly is the acute fatal dose for a human being weighing 70 kg., while 20 mg.  $V_2O_5$  can be safely given subcutaneously or intramuscularly. The *dosis tolerata* and the *dosis toxica* of sodium tetravanadate are very close. Doses of 10 mg.  $V_2O_5$  intravenously can be given safely over a long period without any untoward symptoms. The intramuscular application of 10 mg. or 20 mg.  $V_2O_5$ , when properly injected, causes very little infiltration, without any tendency to suppuration.

The safe dose of sodium hexavanadate for man is 60 mg.  $V_2O_5$ ; for woman, about 40 mg.  $V_2O_5$ . The method of administration apparently does not make any difference in dosage, at least it has not in our short experience. The injections should be stopped when anorexia or signs of renal irritation appear. These symptoms usually subside in a few days, and subsequent injections are borne well. As yet the first dose has never produced these symptoms. After the second, or subsequent injection, signs of intolerance have appeared. While sodium tetravanadate in the proper dose is but slightly irritating to the connective tissue, sodium hexavanadate, given intramuscularly, may occasionally cause swelling and pain, which, however, will yield in a few days to wet dressings. The intravenous injection should be carried out with the greatest care, so that none of the solution may escape into the subcutaneous tissue. The intramuscular injection of the hexa-

vanadate may at times cause severe irritation after the third injection, but no tendency to suppuration was observed and the infiltration resulting from the injection is spontaneously resolved in from three to seven days. The intravenous injection is, therefore, preferable.

One hundred to 120 mg.  $V_2O_5$  as sodium hexavanadate, must be regarded as the toxic dose, since severe reactions, such as nausea and vomiting, begin a few hours after the injection and persist for about 36 hours, sometimes accompanied by an increase in temperature (in one case  $102^\circ$  F.), and albuminuria and cylindruria. These symptoms subside spontaneously in a few days. With sodium hexavanadate, three to four times as much  $V_2O_5$  can be introduced into the body as with sodium tetravanadate without the danger of severe symptoms such as collapse and dyspnea, which follow the injection of excessive doses of tetravanadate.

In cases of collapse and danger of respiratory paralysis, which was observed in but one case in our earlier work with sodium tetravanadate, artificial respiration and a subcutaneous injection of caffeine relieved the symptoms very quickly. Since vanadium in toxic doses lowers the temperature, the patient should be well covered and hot water bags applied. The recovery from vanadium poisoning is usually quite rapid, and no symptoms of injury to the central nervous system, cardiovascular apparatus, or intestines are observed. The kidney irritation subsides in a few days. Permanent damage to the kidneys is unlikely, since animal experiments have shown that a complete regeneration of the secretory epithelium without interstitial changes takes place.

In cases of acute intoxication it must be remembered that vanadium is excreted mainly through the intestines, and since the drug causes increased peristalsis, the bowels usually act very promptly when a large dose is administered, causing the evacuation of a large part. To remove all the vanadium, a saline cathartic may be given.

The urine should always be carefully examined before the drug is given and signs of nephritis should be regarded as a contraindication. The urinary findings should also be watched during the administration of the drug.

## EFFECT OF VANADIUM ON PRIMARY AND SECONDARY SYPHILIS IN MAN

The most striking effect of vanadium was observed in experimental syphilis in rabbits. Since a complete sterilization of rabbits with serotum syphilis was possible, it was logical to apply vanadium to human syphilis. For this purpose, primary and secondary syphilitic cases in which the presence of spirochete pallida could be readily demonstrated by the dark-field illuminator, were injected either intravenously or intramuscularly with vanadium.

Tables XIV and XV show the effect of sodium tetravanadate on spirochete pallida and syphilitic lesions.

TABLE XIV

EFFECT OF SODIUM TETRAVANADATE ON SPIROCHETE PALLIDA				
Case No.	Lesion	First Dose	Second Dose	Interval Before Spirochetes Disappeared
1	Moist papule	10 mg. intravenous		24 hours
2	Flat condyloma	10 mg. intravenous	Fifth day, 10 mg. intravenous	24 hours
3	Chancre	10 mg. intravenous	Third day, 10 mg. intravenous	48 hours
4	Mucous patch	10 mg. intravenous		24 hours
5	Moist papule	10 mg. intravenous	Second day, 10 mg. intravenous	24 hours
9	Mucous patch	10 mg. intravenous		24 hours
11	Mucous patch on tonsil	10 mg. intravenous		24 hours
	Moist papule near anus			
17	Moist papule	10 mg. intravenous	Fourth day, 20 mg. intramuse.	24 hours
18	Flat condyloma	10 mg. intravenous		48 hours
19	Chancre	20 mg. intramuse.		48 hours
22	Flat condyloma near anus			
	Moist papule on penis	20 mg. intramuse.		32 hours

The injection of 10 to 20 mg.  $V_2O_5$  as sodium tetravanadate causes a disappearance of the spirochete in twenty-four to forty-eight hours. The syphilitic lesions cleared up in 2 to 16 days after the injection

TABLE XV

EFFECT OF SODIUM TETRAVANADATE ON SYPHILITIC LESIONS					
Case No.	Lesion	Improved	Cleared*	Method and Amount of Treatment	Total Amount Injected
1	Mucous patches	1 day	5 days	10 mg. intravenous	10 mg.
2	Flat condyloma	5 days	11 days	4 of 10 mg. intravenous	40 mg.
3**	Multiple chancres	No improvement in 7 days.		4 of 10 mg. intravenous	40 mg.
4	Mucous patches	2 days	4 days	2 of 10 mg. intravenous	20 mg.
	Papulopustular eruption and laryngitis	5 days	10 days almost cleared	3 of 10 mg. intravenous	30 mg.
5	Moist papules	1 day	5 days	2 of 10 mg. intravenous	20 mg.
6	Mucous patches	1 day	3 days	2 of 20 mg. intramusc.	40 mg.
7	Mucous patches	1 day	2 days	10 mg. intravenous	10 mg.
9	Mucous patches	1 day	3 days	10 mg. intravenous	10 mg.
10†	Corymbose flat papular	5 days		20 mg. and 10 mg. intramusc.	30 mg.
11	Mucous patches	2 days	3 days	2 of 20 mg. intramusc.	40 mg.
12	Mucous patches	1 day	3 days	10 mg. intravenous	10 mg.
	Moist papule	2 days	7 days	3 of 10 mg. intravenous	30 mg.
13	Moist papules	3 days	9 days	2 of 20 mg. intramusc.	20 mg.
14	Mucous patches	2 days	5 days	2 of 10 mg. intravenous	20 mg.
	Roseola	5 days	11 days		
	Condylomata	5 days	9 days	3 of 10 mg. intravenous	30 mg.
15	Papulopustular	19 days		3 of 10 mg. and 3 of 20 mg. intramusc.	90 mg.
16	Flat papular	5 days	8 days	1 of 20 mg. and 1 of 10 mg. intravenous	30 mg.
17	Circinate papular	2 days	6 days	10 mg. intravenous	
				20 mg. intramusc.	30 mg.
18	Flat condylomata	5 days	16 days	2 of 10 mg. intravenous	
				3 of 20 mg. intramusc.	80 mg.
	Roseola		10 days	same as above	80 mg.
19	Chancre and roseola	8 days		3 of 20 mg. intramusc.	60 mg.
20	Gummata of leg	13 days		7 of 20 mg. intramusc.	140 mg.

\*This means that the mucous patches and roseola have disappeared, and the papular lesions and condylomata have been reduced to macules.

\*\*Treatment discontinued because of intolerance to drug.

†The lesions slowly receded to pigmented macules after 22 injections, mostly intravenous. In the course of 2 months, new lesions appeared encircling the original patches.

of 10 to 140 mg.  $V_2O_5$ . On account of the toxicity of sodium tetra-vanadate the treatment with this salt was abandoned, and a new series of cases was treated with sodium hexavanadate. Table XVI gives the dosage of sodium hexavanadate and the time of disappearance of the spirochete in eleven cases of primary and secondary syphilis.

The table demonstrates that in three cases injected intravenously with 40 mg.  $V_2O_5$  the spirochetes disappeared in two cases in 18 and 22 hours, while they were still present in the third case after 42 hours. In seven cases injected intramuscularly with from 30 to 80 mg.  $V_2O_5$ ,

TABLE XVI

EFFECT OF SODIUM HEXAVANADATE ON SPIROCHETE PALLIDA						
Case No.	Sex	Approximate Weight	Lesion	First Dose	Second Dose	Interval Before Spirochete Pallida Disappeared
1	Woman	150 lbs.	Chanere lip	30 mg. intramusc.		48 hours
2	Woman	110 "	Flat condyloma	30 mg. intramusc.		23 hours One spirochete found after long search
3	Man	150 "	Mucous patch	40 mg. intramusc.		42 hours
4	Man	135 "	Flat condyloma	80 mg. intramusc.		48 hours
5	Man	150 "	Chanere lip	80 mg. intramusc.		42 hours
6	Man	125 "	Flat condyloma	80 mg. intramusc.	After 2 days 80 mg. intramusc.	18 hours after second injection
7	Man	125 "	Flat condyloma	80 mg. intramusc.		24 hours
13	Man	160 "	Chanere	55 mg. intramusc.		28 hours
14	Man	135 "	Moist papule	40 mg. intravenous		22 hours
15	Man	135 "	Moist papule	40 mg. intravenous		18 hours
20	Boy	110 "	Flat condyloma	40 mg. intravenous		Still present after 42 hours

the spirochetes disappeared entirely in 24 to 48 hours. In one of these, which received 30 mg.  $V_2O_5$ , very few spirochetes were found after 23 hours. In Case No. 6, after the injection of two doses of 80 mg. each, the spirochetes disappeared 18 hours after the second injection. Cases No. 14 and No. 15 indicate that the larger doses administered intravenously, which we feared to give at the time these cases were treated, may prove still more effective. Without any perceptible difference either in clinical appearance, number and activity of spirochetes or strength of Wassermann reaction, some cases (Case No. 6) prove more resistant than others and require a second dose to eradicate the organisms.

The moist secondary lesions invariably showed a rapid improvement whether treated intravenously or intramuscularly. The dry lesions were not so quickly affected, but showed improvement in about a week. Table XVII shows the amounts of  $V_2O_5$  injected as hexavanadate and the time required to improve and clear up the lesions in twelve cases of secondary syphilis.

TABLE XVII

EFFECT OF SODIUM HEXAVANADATE ON SYPHILITIC LESIONS					
Case* No.	Lesion	Improved	Cleared**	Method and Amount of Treatment	Total Amount Injected
4	Mucous patches	1 day	3 days	2 of 80 mg and 1 of 100 mg. intramusc.	260 mg.
6	Flat condylomata	4 days	10 days	2 of 80 mg. intramusc., then other treatment given	160 mg.
7	Flat condylomata	3 days		2 of 80 mg. intramusc., then put on other treatment	160 mg.
8	Papulopustular	10 days	23 days	1 of 55 mg., 2 of 80 mg. intramusc., 2 of 30 mg., 2 of 60 mg., 3 of 80 mg. intravenous	635 mg.
9	Moist papules	3 days	9 days	3 of 80 mg. intramusc., 1 of 40 mg. intravenous	280 mg.
10	Pigmented maculo- papular	12 days	17 days	3 of 80 mg. intramusc.; 3 of 40 mg. and 1 of 60 mg. intravenous.	420 mg.
11	Flat condylomata	5 days	13 days	2 of 55 mg. intramusc.; 1 of 40 mg., 2 of 30 mg. and 1 of 60 mg. intravenous	270 mg.
12	Flat papular	4 days	10 days	1 of 40 mg., 2 of 30 mg., and 1 of 60 mg. intravenous	160 mg.
14	Flat papular	6 days	13 days	1 of 40 mg., 1 of 30 mg., 2 of 60 mg. and 1 of 80 mg. intravenous	270 mg.
15	Moist papules	2 days	11 days	1 of 40 mg., 1 of 30 mg., 2 of 60 mg. and 1 of 80 mg. intraven.	270 mg.
16	Moist papules	3 days	5 days	1 of 40 mg. and 1 of 30 mg. intravenous	70 mg.
18	Mucous patches	1 day	3 days	1 of 40 mg., 1 of 30 mg. and 2 of 60 mg. intravenous	190 mg.
	Laryngitis	1 day	5 days		
	Flat papular	4 days	9 days		

\*Cases 13 and 17 were omitted from this table because they were primary cases which we did not feel justified in treating with vanadium alone, but added mercury in the hope of aborting the disease. This hope seems to be justified in case 13. Case 17 left the hospital in spite of our protests.

\*\*By this is meant that mucous patches have disappeared and other lesions have become macular.

Mucous patches, moist papules, and flat condylomata were cleared up in from three to thirteen days. In one case a laryngitis was cleared up in five days. Flat papular and papulopustular eruptions required from thirteen to twenty-three days. The total amount of vanadium given ranged from 110 to 635 mgs. as  $V_2O_5$ .

*Effect of Sodium Hexavanadate on the Wassermann Reaction.*—The short time during which we have been able to follow our cases has made it impossible to show any permanently negative reactions, but we believe we have observed a definite weakening of the reaction in a very short time, as Table XVIII shows. The amount of serum given is the smallest amount with which a strongly positive reaction occurred. The maximum amount of serum used in the Wassermann is 0.2 c.c. and the usual early secondary case titrates .02 or .01 c.c.; that is, even this small amount of serum gives a strong positive reaction. As seen in the table, the titer rises during treatment from .01 or .02 to .05, 0.1, or 0.2 c.c. serum. Only when it becomes negative with the maximum amount of serum, 0.2 c.c., (as in Case No. 4, Second W. R.) does it become a negative serum.

Several cases lost some of the gain they had made during an interval in which they received no treatment because of sore arms.

Case No. 15 is noteworthy. The spirochetes yielded in eighteen hours to a small intravenous injection; but after nine intravenous injections, the Wassermann reaction remained as strong as at the beginning. This failure to get a prompt effect was explained by examination of the spinal fluid, which gave a positive Nonne reaction and a strong positive Wassermann.

TABLE XVIII  
EFFECT ON WASSERMANN REACTION

Case No.	Stage of Disease	First W. R.	Interval	Second W. R.	Interval	Third W. R.
4	Secondary	Strong + with 0.1 c.c.	18 days	Negative with 0.2 c.c.	8 days—No treatment	Weak + with 0.2 c.c.
6	Secondary	Strong + with 0.01 c.c.	18 days	Strong + with .05 c.c.		
8	Early secondary	Strong + with .005 c.c.	11 days	Strong + with .02 c.c.	19 days	Strong + with 0.5 c.c.
10	Early secondary	Strong + with .01 c.c.	19 days	Strong + with 0.1 c.c.	No treatment—12 days	Strong + with .05 c.c.
11	Early secondary	Strong + with .02 c.c.	15 days	Strong + with 0.2 c.c.	No treatment—12 days	Strong + with 0.1 c.c.
12	Early secondary	Strong + with .02 c.c.	11 days	Strong + with 0.1 c.c.	Little treatment—12 days	Strong + with 0.1 c.c.
15	Secondary	Strong + with .01 c.c.	21 days	Strong + with .01 c.c.		



Of the seven cases in which we were able to follow the Wassermann reaction for two weeks or longer, six showed a definite weakening of the strength of the reaction. The seventh case, which showed absolutely no effect upon the Wassermann reaction after three weeks' treatment, belongs to the class of cases in which the Wassermann is often resistant to all treatment.

We cannot conclude this report without cordially thanking Drs. E. W. Bedford, E. C. Troxell, P. J. Murphy, H. H. Freilich, W. D. Holmers, J. W. Thornton, G. H. Robbins, and C. W. Robertson, all members of the resident staff of the Cook County Hospital, for the active cooperation which has made this research possible.

*Summary.*—Sodium hexavandate is a soluble neutral salt readily sterilized in solution and therefore capable of being put up in ampules ready for injection. It causes no irritation of the mucous membrane of the mouth, and we therefore have been able to treat with it patients whose bad mouth conditions would have made mercurial treatment very difficult, if not impossible.

The appearance of albumin and casts in the urine, or of anorexia or slight nausea, indicate intolerance to the drug, and call for an intermission in treatment. These symptoms may be delayed until the second day after injection, so that a three day interval should be allowed between doses.

Our brief experience warrants the conclusion that the salts of vanadium have a specific effect on syphilis, quickly rendering harmless the dangerous moist lesions of the first two stages, clearing up the clinical manifestations and favorably affecting the Wassermann reaction. Definite conclusions as to their value in comparison to the other anti-syphilitics now in use will require a much longer experience.

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# A PROCEDURE FOR SERUM DIAGNOSIS OF SYPHILIS ESPECIALLY RECOMMENDED FOR HOSPITAL ROUTINE\*

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IN 1901 Bordet and Gengou<sup>1, 2</sup> described a method for detecting the presence of specific antibodies in the serum by means of complement fixation. Five years later the principle of this method was successfully applied by Wassermann, Neisser and Bruck,<sup>3</sup> and independently by Detre,<sup>4</sup> to the serum diagnosis of syphilis. From the beginning it was realized that the results obtained by this test were not always reliable. Because the test gave a great deal of valuable information, however, it was not discarded, but many workers attempted to modify it to make it more accurate.

One year after the Wassermann reaction was first described, Marie and Levaditi<sup>5</sup> discovered that it was not specific in the true sense since it was not necessary to start with syphilitic tissue in order to get a satisfactory antigen. This observation was quickly confirmed by many other investigators.

The fact that there is often present a considerable amount of anti-sheep amboceptor in normal human serum was also early noted. Because of the uncontrollable variations in this factor it is very difficult to maintain correct quantitative relations between all the reagents used in the test, which condition is an absolute prerequisite to the proper performance of the Wassermann reaction.

In the technic as originally described it was necessary to inactivate the human serum to be tested in order to destroy its normal complement. This inactivation was found to remove to a great extent, the specific complement-fixing properties of the serum.

With these and other objections in view, the Wassermann reaction was studied very intensively by many workers and various changes

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in the method were suggested in the attempt to eliminate errors. Even at the present day, eleven years after the introduction of the Wassermann reaction, there is a definite movement toward standardizing this reaction. It is thus tacitly acknowledged that almost every worker uses a different method depending on the laboratory in which he received his training and the care and skill with which he performs the test. The errors inherent to individual modifications are well known, but are ignored and claimed to be unimportant by the advocates of each method. In their attempts to make the reaction more useful some of the workers have erred on the side of making it too delicate, thus obtaining fixation of complement with the sera of others than syphilitics. Some of the methods which are accurately enough adjusted so as to avoid this error of nonspecific fixation, require so much work in connection with each serum that they are not applicable to routine work. Our experience with different modifications in the course of the last ten years prompts us to suggest a method which will largely avoid the errors inherent to those in use. While being very delicate and detecting even very small amounts of antibody in the serum, our procedure is nevertheless not over sensitive, is not too cumbersome and can be very easily applied in testing a number of cases at one time. Before giving the description of this procedure, it might be well to point out the disadvantages of some of the other methods, which disadvantages we avoid in our modification.

One of the earliest objections to the original Wassermann technic was that the quantitative relations between the different reagents was very much disturbed on account of the variable amount of natural antish sheep amboceptor present in the blood of different individuals. To correct this it was suggested by different authors to either remove this amboceptor by means of adsorption with barium sulphate or to extract it (in the ice box) with corresponding red blood cells. Some authors proposed to measure the amount of natural amboceptor in the human serum and correct its deficiency by the addition of suitable amounts of corresponding artificial amboceptor. However, these corrections did not solve the difficulty altogether. The adsorption with barium sulphate, although it removes the excess of natural hemolytic amboceptor, also removes some of the specific antibody,<sup>6</sup> and for this reason such procedure is not to be recommended. Extraction of natural amboceptor with cells is more practical but requires addi-

tional work preliminary to the test proper and often leads to partial hemolysis of the cells, making the final reading of the reaction more difficult. Besides, the preliminary titration of the natural hemolytic amboceptor is satisfactory only in cases where the amount of amboceptor is small and more can then be added to bring the amount up to that necessary in the test. If, however, there is an excessive amount of antish sheep amboceptor originally present in the serum (which is not unusual) the complication can not be removed as easily. To obviate this interference by the natural antish sheep amboceptor many workers attempted using red blood cells from other sources than the sheep, against which natural amboceptors are not so common. Thus, Browning and McKenzie<sup>7</sup> suggested ox cells; Tschernogubow,<sup>9</sup> guinea pig; Detre and Brezowski, horse. Natural amboceptors for all these cells are rarer in the human serum than that against sheep cells, but still are quite often found. Noguchi<sup>8</sup> and Tschernogubow<sup>9</sup> finally suggested the use of human cells, for the chances for antihuman hemolytic amboceptor to be present in human serum are practically nil. It is for this reason that in our modification we also use the antihuman hemolytic system. The objection commonly raised against the use of human cells is that they were not as conveniently obtained as those of an animal, unless the serologist obtains them by pricking his own finger, which is not a pleasant daily duty. This difficulty can be successfully obviated by obtaining the cells from the freshly collected clotted blood of the patient. However, the standardization of a suspension of cells obtained in such a manner offers a source of much variation. We have devised a method whereby one can easily titrate the strength of an unknown suspension of human cells made from a broken up clot.

Another disadvantage of the original procedure which has been retained in the majority of subsequent modifications is the inactivation which was originally advocated for the purpose of removing the complement from the patient's serum. It was shown, however, that heating of a fresh serum containing antibodies, for  $\frac{1}{2}$  hour at  $56^{\circ}\text{C}$ ., while it destroys the complement, also reduces the concentration of antibodies from three to five times.<sup>8, 10</sup> For this reason several authors have advocated the use of fresh serum for the test. In our method we also employ unheated serum, in order to conserve all the antibody. Certain workers use unheated serum, but ignore the natural comple-

ment present and add to it the complement from the guinea pig.<sup>8</sup> We have found that this may lead occasionally to error, especially if one uses sensitized cells for the test. The use of the complement of the human serum alone, without the addition of guinea pig complement (as recommended in other modifications)<sup>11, 12</sup> seems inadvisable because the amount of it in individual fresh sera varies markedly, and in older sera the complement may be absent entirely. Gradwohl,<sup>13</sup> realizing the fluctuations in the quantity of the natural antisheep amboceptor and of complement in the human serum suggests a preliminary titration of the hemolytic power of human serum. His titration, however, determines only the strength of the hemolytic complex (amboceptor plus complement) but not of individual elements. Such procedure has a disadvantage in that sera, having similar hemolytic indices, may contain dissimilar respective amounts of amboceptor and of complement available for the fixation test.

In our procedure we make use of the complement present in human serum, but we titrate it with antihuman amboceptor and cells, and add guinea pig complement when necessary.

It has been suggested by Stitt<sup>14</sup> that the use of sensitized cells for the final reading of fixation of complement gives quicker and more clean cut results. In addition to these advantages we found that use of the sensitized cells permits of employing a very small amount of complement, as a given volume of sensitized cells is hemolyzed by a much smaller amount of complement than it would take to hemolyze the same amount of cells if the complement and amboceptor were added to them at the same time.<sup>15</sup> If the amount of complement used in the test be thus reduced, it can be fixed in the presence of a weakly positive serum, whereas a larger amount would not be, and thus the test may be rendered more delicate.\*

**PREPARATION OF REAGENTS.**—Before describing details of the method a word must first be said about obtaining and standardizing of reagents.

*Human Cells.*—The suspension of human red blood cells is made from the clot of any freshly taken blood, except that from patients suffering from hematogenous diseases. It does not make any difference whether the blood is derived from a syphilitic or not, provided

\*It must be kept in mind that guinea pig serum sometimes has natural antihuman and antisheep amboceptor present in it and the use of such serum for complement brings in another source of error. In our method the amount of guinea pig serum used is so small that this source of error is reduced to a minimum.

the cells are washed free from serum. The clot is shaken with physiological salt solution in a test tube, and the liberated cells are filtered through a filter paper.\* After filtering, the red blood cells are washed by repeated centrifuging and decantation, until the serum is all washed away. The density of the suspension is then titrated by means of a Sahli hemoglobinometer. The pipette supplied with this instrument holds sufficient blood (0.02 c.c.) to give a reading of 80 with normal blood of men, and 70 with normal blood of women. Placing the average reading for 0.02 c.c. of 100% human blood at 75, we test our suspension of unknown concentration of cells just as if it were whole blood. According to the reading we obtain we can calculate the strength of this unknown suspension and dilute it to any desired density.\*\*

*Hemolytic Amboceptor.*—As stated above we use in this modification the antihuman hemolytic system. The antihuman amboceptor is prepared by repeated injection of rabbits with washed red cells.† The washed human blood is injected intravenously into rabbits at four day intervals. In order to avoid anaphylactic reactions, each intravenous injection, beginning with the third one, is preceded by a desensitizing intraperitoneal injection of the same cells given one-half hour in advance. Nine to ten days after the fourth or fifth injection some of the blood of the rabbit is removed and tested. If the titer is found to be suitable the rabbit is bled from the carotid artery. Forty to fifty cubic centimeters of blood can be easily obtained from each rabbit without killing the animal. The serum containing amboceptor, after separation from the clot, is quickly dried on paper *in vacuo* and preserved in this form. Before use a portion of the dry

\*One must be careful to use paper which is free from acids. So-called acid-washed paper may retain enough acid to weaken the cells. We recommend C. S. & S. No. 588 filter paper.

\*\*As an example: The reading with the unknown suspension may be 50. This means that the suspension is 50/75 or 66.6% of whole blood. To make a 10% suspension dilute 1.0 c.c. of the stock up to 6.66 c.c. with physiological salt solution. To make a 50% suspension dilute 5.0 c.c. to 6.66 c.c. and so on. We make a stock 50% red blood cell suspension and dilute further as will be shown later.

†For this purpose nine volumes of human blood are collected from the vein into a container having in it one volume of sterile 2% sodium citrate solution (in 0.85% sodium chloride) to prevent coagulation of the blood. The cells are then washed by repeated centrifugation and decantation of supernatant fluid which in the first two washings consists of sterile physiological salt solution containing 0.2% of sodium citrate and later pure sterile physiological salt solution. Care should be taken to continue the washings until the supernatant salt solution is serum free. This can be determined by testing it with acetic acid and heat which will disclose less than one part of albumin in 60,000. This precaution, which is useful when any amboceptor is prepared, is of especial importance in the preparation of antihuman amboceptor. The injection of even traces of foreign serum together with the cells into rabbits results in production of specific precipitins along with hemolysins. When later human serum is used in the test it may combine with the antihuman precipitin contained in the rabbit's serum and thus use up a part of the complement available in the test.



amboceptor is taken up in a suitable volume of physiological salt solution determined by preliminary titration.

This titration is performed as follows: Place in several test tubes (see Table I) varying amounts of amboceptor solution and bring up the volume to 0.8 c.c. with physiological salt solution, then add 0.2 c.c. of the 50% suspension of washed human red blood cells. Incubate for one-half hour in the water bath at 37°C., shaking occasionally. This results in 1.0 c.c. of a 10% suspension of red blood cells sensitized with varying amounts of amboceptor. At the end of the half hour allowed for sensitization distribute 0.025 c.c. of fresh human serum (human complement) into as many test tubes as there are dilutions of amboceptor above, and bring up the volume in each of these tubes to 0.9 c.c. These tubes then each receive red blood cells sensitized with gradually decreasing amounts of amboceptor. (This is done by transferring to each of them 0.1 c.c. from the various tubes above.) We have then a series of tubes each containing 1.0 c.c. of 1% suspension of blood cells sensitized in the presence of varying amounts of amboceptor, and 0.025 c.c. of human serum. Incubate them at 37°C. for one-half hour and read the amount of hemolysis in the tubes. The smallest amount of amboceptor which will sensitize 0.1 c.c. of 10% red blood cells so that they are completely hemolyzed by 0.025 c.c. of fresh human serum constitutes one unit of amboceptor. This titration should be repeated with many fresh human sera and the average unit found should be considered as the standard of this batch of amboceptor.

The amboceptor keeps fairly well, and the unit thus determined has to be only occasionally verified to detect any possible deterioration. In this way we adjust this system so that there is one unit of complement in 0.025 c.c. of the average fresh human serum. In the actual test we use 0.05 c.c. of human serum and thus can have no more than two units of complement present. Of course, individual specimens of human serum may vary somewhat in the complement content. We have selected 0.025 c.c. of human serum as one complement unit, after testing many fresh human sera and finding that the great majority of them will not have sufficient complement to hemolyze 1.0 c.c. of 1.0% red blood cells in less than this amount, even if an excess of amboceptor is used to sensitize the cells. In such cases, where the amount of complement is above the average, the variation was

TABLE I

TUBE NUMBER	I	II	III	IV	V	VI
Red blood cells 50% suspension.....	0.2 c.c.	0.2 c.c.	0.2 c.c.	0.2 c.c.	0.2 c.c.	0.2 c.c.
Salt solution 0.85%...	0.1 c.c.	0.2 c.c.	0.3 c.c.	0.4 c.c.	0.5 c.c.	0.6 c.c.
Amboceptor solution .	0.7 c.c.	0.6 c.c.	0.5 c.c.	0.4 c.c.	0.3 c.c.	0.2 c.c.
Incubated for 30 minutes at 37° C.						
0.1 c.c. of sensitized cells out of Tube No.	I	II	III	IV	V	VI
Salt Solution 0.85%...	0.65 c.c.	0.65 c.c.	0.65 c.c.	0.65 c.c.	0.65 c.c.	0.65 c.c.
Fresh Human Serum (Complement) diluted 1:10.....	0.25 c.c.	0.25 c.c.	0.25 c.c.	0.25 c.c.	0.25 c.c.	0.25 c.c.
Incubated for 30 minutes at 37° C.						
Results.....	CH	CH	CH	FCH	TrH	NoH

CH=Complete Hemolysis; FCH=Fairly Complete Hemolysis; TrH=Trace of Hemolysis; NoH=No Hemolysis.

found to be usually within a fraction of a unit. In cases\* where there is less than one unit of complement in 0.025 c.c. or two units in 0.05 c.c. (the amount used in the test), we correct this deficiency by adding the proper amount of guinea pig complement.

*Guinea Pig Complement.*—Having standardized the amboceptor, one can determine the unit of guinea pig complement. We obtain the complement by bleeding guinea pigs from the ear. The guinea pigs are kept hungry for two to three hours before bleeding. With a little patience one can easily obtain 5 to 6 c.c. of blood from a guinea pig's ear. Three cubic centimeters of blood will give more than enough complement to perform 100 to 150 tests by our method. We usually bleed several guinea pigs from the ear, taking from each about 1 c.c. of blood. This equalizes the differences in the complement titers of

\*We repeatedly noticed that sera from syphilitics or from cases showing high fever or severe infection of any kind have deficiency in complement and what complement is present very quickly disappears from the serum on standing.<sup>16</sup>

different guinea pigs,<sup>17</sup> and also leaves our stock of animals practically intact. To titrate the guinea pig complement one places 10 units of amboceptor, as determined above, in a test tube, brings the volume up 0.8 c.c. with physiological salt solution, and adds 0.2 c.c. of 50% red blood cells (10 units). The tube is incubated at 37°C., for one-half hour (see Table II). Meantime one places various dilutions of guinea pig serum in a series of test tubes and brings the volume to 0.9 c.c. with physiological salt solution. At the end of the half hour for sensitization one adds 0.1 c.c. of the sensitized cells to each of these

TABLE II

10 UNITS OF AMBOCEPTOR (IN 0.8 C.C. OF SALT SOLUTION)+ 0.2 C.C. OF 50% WASHED RED BLOOD CELLS							
Result	Incubated 30 minutes at 37° C.						
	Sensitized cells.						
Guinea pig serum 1%.	0.9 c.c.	0.8 c.c.	0.7 c.c.	0.6 c.c.	0.5 c.c.	0.4 c.c.	0.3 c.c.
Salt solution 0.85%.	0.0 c.c.	0.1 c.c.	0.2 c.c.	0.3 c.c.	0.4 c.c.	0.5 c.c.	0.6 c.c.
Sensitized red blood cells.....	0.1 c.c.	0.1 c.c.	0.1 c.c.	0.1 c.c.	0.1 c.c.	0.1 c.c.	0.1 c.c.
Results.....	Incubated 30 minutes at 37° C.						
	CH	CH	CH	FCH	TrH	NoH	NoH

tubes, and incubates the tubes for one-half hour. At the end of incubation one estimates the amount of hemolysis in each tube of the series. The amount of complement in the tube just showing complete hemolysis designates one unit of guinea pig complement. We call this amount of guinea pig complement human equivalent unit (HEU); i. e., this amount of guinea pig complement is equivalent in its hemolytic activity to the amount of complement found in 0.025 c.c. of the average fresh human serum. We have found that HEU of guinea pig complement is usually contained in 0.007 c.c. of fresh guinea pig serum. Owing to the individual variation in the sera of

different guinea pigs, it is necessary to make this titration each day, using the unit of amboceptor as a constant.

*Antigen.*—The antigen is the acetone insoluble fraction of alcoholic extract of normal beef heart made essentially as described by Noguchi and Bronfenbrenner.<sup>18</sup> We found recently that it is possible to prepare this antigen in such a way that 1/10 of the anticomplementary dose of it contains from ten to one hundred antigenic units (depending upon the serum against which it is tested). The antigen is titrated in the usual manner with the difference that its anticomplementary dose is determined against one HEU of guinea pig complement and one unit of amboceptor.

With properly titrated reagents ready, one proceeds to carry out the test. To save time and reagents, when examining a large number of specimens, we find it possible to eliminate many negative sera by a crude presumptive test. Such a test, naturally, must be adjusted so as to be hypersensitive in order not to miss the reaction in any positive case. Of course, adjusted in this way, the test is bound to give positive reactions in some negative cases, but such a presumptive test has great value in that it eliminates the majority of negative cases. We use several devices to make this test very sensitive. To begin with, no complement is added to what may be present in the human serum: one-third (instead of one-tenth) of the anticomplementary dose of the antigen (from 30 up to over 300 antigenic units) is used, and incubation is carried out in the ice box for 18 hours. This exclusion test (see Table IV—Presumptive Test) is performed as follows:

**PRESUMPTIVE TEST.**—Each serum to be tested is placed in a tube in the quantity of 0.05 c.c., the proper amount of antigen is added, and the total volume is brought up to 0.9 c.c. with physiological salt solution. The series is placed into the ice box overnight (18 hours), and at the end of this period the tubes are warmed up by placing them into a water bath for one-half hour. While the tubes are being warmed up, one sensitizes the cells in the following way. Enough amboceptor is diluted with physiological salt solution so that 10 hemolytic units are represented by 0.8 c.c. of solution and 0.2 c.c. of 50% red blood cells (10 units) are added to each ten units of amboceptor. This results in obtaining a 10% suspension of cells in 1 c.c. of amboceptor solution. At the end of a half hour 0.1 c.c. of this 10% sus-

pension of sensitized cells is added to each of the tubes, after which they are incubated at 37°C. for another half hour. Complete hemolysis in a given tube indicates the absence of specific antibody in the serum tested and nothing further need be done with such serum. If the hemolysis is not complete the serum must be further subjected to a more accurate test. The incompleteness of hemolysis in the presumptive test can be attributed to either of two causes. First, the serum might have contained less than one unit of complement in the amount used (0.05 c.c.).\* Second, there might have been enough complement present in the patient's serum to complete the hemolysis, but it might have been fixed, due to the simultaneous presence of specific antibody.

*Titration of Human Complement.*—In order to ascertain which of the two causes of incomplete hemolysis was operating in the presumptive test above, one proceeds to determine how much complement is present in such sera. Of each serum having shown incomplete or total absence of hemolysis one places 0.025 and 0.05 c.c. in two tubes respectively and brings the volume of each up to 0.9 c.c. with physiological salt solution; one adds to each tube 0.1 c.c. of a 10% suspension of sensitized human red blood cells (prepared as described above) and incubates the tubes in a water bath at 37°C. for 1½ hour. The amount of hemolysis in each tube is then noted. This titration may indicate the following possibilities:

TABLE III

VARIOUS POSSIBILITIES IN THE DEGREE OF HEMOLYSIS OBTAINED IN COMPLEMENT TITRATION EXPERIMENT (DETERMINED BY MADSEN SCALE).		NUMBER OF UNITS OF COMPLEMENT PRESENT IN 0.05 C.C. OF SERUM AS DETERMINED BY TITRATION.
0.025 c.c. serum	0.05 c.c. serum	
0% hemolysis	0% of hemolysis	0.0
0% "	50-75% "	0.5
0-50% "	75-100% "	1.0
50-75% "	100% "	1.5
75-100% "	100% "	2.0

\*We find that some sera are devoid of complement in the amount of 0.05 c.c. of serum, already within the first 24 hours after the blood is taken.<sup>18</sup> This is especially true, as stated above, in acute infectious diseases and also in syphilis. For this reason we feel that it is dangerous in performing the Wassermann reaction to depend on human complement exclusively even if all the other factors (such as presence of natural amboceptor, etc.) are well taken care of. We wish to emphasize that the presumptive test, as we describe it above, or other similar modifications, should never be relied upon otherwise than as a method of excluding the majority of negative cases.

One may obtain no hemolysis in either tube (see Table III) which indicates that there is only a fraction of a unit or no complement in 0.05 c.c. of the serum (the amount used in the test). On the other hand, one may obtain complete hemolysis in both tubes which would mean that 0.025 c.c. of the serum contained at least one unit of complement, or 0.05 c.c. two units.\* The variations between these two extremes, although they can be very numerous, for practical purposes can be separated into three groups. When there is no hemolysis in the tube containing the smaller amount of serum (0.025 c.c.) and partial hemolysis (50-75%) in the other tube, we interpret such a result as meaning that there is approximately one-half unit of complement present in 0.05 c.c. of such serum. If the tube containing 0.05 c.c. of serum shows complete or fairly complete hemolysis (75-100%) and with 0.025 c.c. one obtains less than 50% (0-50%) hemolysis, it is considered to mean that 0.05 c.c. of serum contains only one unit of complement. Finally when in the smaller amount of serum (0.025 c.c.) there is partial hemolysis (50-75%), and, of course, complete hemolysis in the larger volume (0.05 c.c.), the amount of complement in 0.05 c.c. of the serum is taken to be 1.5 units.

In order to make the results of individual tests comparable, in our system we add to those sera containing less than *two* units of human complement (as determined by the titration above) a sufficient number of HEU of guinea pig complement to correct the deficiency.

With the reagents standardized and the amount of complement in each serum determined, one is prepared to perform the test proper with absolute control over the quantitative relationship of all the ingredients. The procedure is as follows:

TEST PROPER.—Place 0.05 c.c. of each serum to be tested into each of two test tubes,† add to both tubes a sufficient number of HEU of guinea pig complement (governed by preliminary titration of the complement in the serum) to have a total of two units of complement present. Add a suitable amount of antigen to one of each pair of tubes, leaving the

\*We found that 0.025 c.c. of fresh human serum practically never contains appreciably more than one unit of complement (if titrated in the presence of cells sensitized with one unit of amboceptor). The possible variation in this direction is well within the limit of a small fraction of a unit.

†If one desires to save the time necessary for diluting and measuring of the serum, one may use two drops from a properly calibrated capillary pipette. However, in such a case the same pipette must be used for measuring the serum in the preliminary titration of its complement. As a rule a separate capillary pipette is used for each case, but if it is desirable to make the results more strictly comparable one ought to use the same capillary pipette for all the sera, washing it thoroughly between measurements. We found, however, that a greater degree of accuracy is obtained with the expenditure of no more time if one uses accurately calibrated pipettes holding 0.1 c.c. (divided into 0.01 c.c.).

other tube without antigen as a control. (The amount of antigen we use in the test is a multiple of one antigenic unit (10-100) and is at least ten times smaller than the quantity which by itself fixes one HEU of complement in the presence of cells sensitized with one unit of amboceptor.) Bring up the total volume in each tube of the series to 0.9 c.c. with physiological salt solution, and incubate in the water bath at 37°C. for one-half hour. The usual controls of the hemolytic system and antigen must, of course, accompany each series. At the same time place the washed red blood cells and amboceptor mixture in the water bath to sensitize the cells. At the end of the half hour incubation add 0.1 c.c. of the sensitized cells to each tube, and place the series again into the water bath for one-half hour. Then read the results. As usual the control tubes should show complete hemolysis and the test itself hemolysis or inhibition according to whether the test is negative or positive.\*

Table IV illustrates a series of cases which exhaust the main possibilities. Serum No. 1 is a negative case which is eliminated in the first presumptive test. Case No. 2 shows no hemolysis in the presumptive test. The titration of complement of this serum shows that there is fully two units of it present originally in the amount used in the test and therefore the inhibition of hemolysis in the presumptive test must have been due to the interaction between the serum and antigen. However, since the presumptive test is very crude and a large excess of antigen is used in performing it, there is a possibility of the summation of nonspecific partial fixations of complement by the various ingredients. To exclude this possibility the examination is repeated with the proper amount of ingredients (see Table IV, Test Proper, second stage) and if the hemolysis is inhibited it should be ascribed to specific fixation. Case No. 3 in the presumptive test also shows no hemolysis. When its complement is titrated it is found to have only 1 unit in 0.05 c.c. Therefore the specificity of the fixation in this case is even more to be questioned than in case No. 2. Such case should be repeated with proper adjustment of the amount of

\*In cases where the control tube shows partial or complete inhibition, it is evidently due to the anticomplementary property of the serum. Such a serum can be heated for 10 minutes at 56° C. and its property of fixing the complement can thus be removed and the test repeated. However, in order not to destroy any of the specific antibody by heating, we prefer to titrate out the anticomplementary property of the serum and in repeating the test proper we add to such a serum, not only two HEU of guinea pig complement but in addition to that the amount of complement which such serum is able to fix by itself. Thus when the test proper is repeated there are two HEU of free complement available for the hemolysis in the control tube.

complement and of antigen (see Table IV, Part III) and the case is considered positive only if the inhibition persists under these conditions. Cases No. 4 and No. 5, showing complete inhibition in the presumptive test, apparently lack complement as shown by their respective titrations (see Table IV, Part II). In such cases fully two HEU of guinea pig complement must be added in the test proper and if fixation persists, the reaction can be considered specific.\*

**ROUTINE PROCEDURE.**—Our routine in testing a series of cases is as follows: The last thing in the evening we set up the presumptive test and place it in the ice box. Next morning this series of tubes is placed in the water bath for one-half hour, and at the same time in a separate tube the cells are mixed with amboceptor and are also set in the water bath for one-half hour to be sensitized. At the end of this half hour 0.1 c.c. of sensitized cells is placed in each of the tubes of the series, the tubes placed again in the water bath and one-half hour later the results are noted. The case showing complete hemolysis in this presumptive test can be immediately reported as negative.\*\*

The other sera must be tested further. We place each serum into four tubes; one tube receives 0.025 c.c. and the remaining tubes 0.05 c.c. One of the tubes containing 0.05 c.c. and the tube containing 0.025 c.c. are used for the titration of the amount of complement present in the patient's serum. At the same time the HEU of the guinea pig complement to be used for this series is determined. When the amount of complement in each of the sera is determined we proceed to set up the test proper.

**ABBREVIATED PROCEDURE.**—When time does not permit to follow up in its entirety the routine procedure described above, which demands in all 21 to 22 hours between the time the blood is taken and the rendering of the report, one can omit the presumptive test and combine the two stages of the test proper. The performance of the test in this manner, although it involves the use of a slightly increased amount of reagents however shortens the time necessary for obtaining a result to one hour. This shortened technic permits the titration of the complement in the human serum and the performance of the com-

\*Such sera, lacking complement, may also occasionally exhibit the power to inhibit the hemolysis by the fresh complement (anticomplementary power). If such should be the case, the control tubes will show incomplete or total absence of hemolysis. These cases must be repeated after a preliminary adjustment of complement as described in a previous footnote.

\*\*We find in a general hospital performing routine tests on patients presenting various pathological conditions, the presumptive test will eliminate 75 to 80% of the cases. Thus, although our method seems lengthy, in fact one can perform the test almost as quickly as by the less accurately adjusted methods.



TABLE IV

PRESUMPTIVE TEST I						TEST PROPER FIRST STAGE (COMPLEMENT TITRATION) II					TEST PROPER SECOND STAGE (COMPLEMENT FIXATION) III				
Case No.	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Human serum (in c.c.).....	0.05	0.05	0.05	0.05	0.05	0.025	0.05	0.025	0.05	0.025	0.05	0.05	0.05	0.05	0.05
Guinea pig complement (in HEU and in c.c.).....															
Antigen (0.1% emulsion in c.c.)	0.3	0.3	0.3	0.3	0.3										
Salt solution 0.9% (in c.c.).....	0.55	0.55	0.55	0.55	0.55	0.875	0.85	0.875	0.85	0.875	0.85	0.75	0.65	0.65	0.65
Incubation.....	On ice overnight										Water bath at 37° C, for 30 minutes				
Sensitized cells 10% (in c.c.)..	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Incubation.....	Water bath 37° C, for 30 minutes					Water bath at 37° C, for 30 minutes					Water bath at 37° C, for 30 minutes				
RESULTS:.....	CH	NoH	NoH	NoH	NoH	CH	CH	NoH	CH	NoH	NoH	CH	NoH	CH	CH

Excluded by the presumption test

plement fixation reaction at the same time and is performed as shown in Table V.

TABLE V

	COMPLEMENT TITRATION		TEST PROPER			CONTROLS			
Serum (in c.c.)....	0.025	0.05	0.05	0.05	0.05	0.05	0.05	0.05	.....
Complement Dilution (1 HEU= 0.1 c.c.).....	.....	.....	.....	0.1	0.2	.....	0.1	0.2	0.1
Antigen 0.1% emulsion (in c.c.).....	.....	.....	0.1	0.1	0.1	.....	.....	.....	0.7
Salt solution.....	0.875	0.85	0.75	0.65	0.55	0.85	0.75	0.65	0.1
Incubation at 37° C, for 30 minutes.									
Sensitized cells 10% suspension (in c.c.).....	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	00.1
Incubation at 37° C, for 30 minutes.									

In carrying out this shortened method one does not wait for the results of the titration determining the amount of complement present in the human serum, but performs the test proper and its controls at the same time. However, in this test instead of using two tubes (the test and its control) each containing the properly adjusted amount of complement, one uses six tubes; one pair receives no extra guinea pig complement, one pair one HEU of guinea pig complement, and one pair two HEU. The results obtained in the test proper must be interpreted in the light of the outcome of the titration of complement.\*

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\*In case the control tubes should indicate that the serum is anticomplementary, one must proceed as described above (footnote, page 417); namely, to adjust the amount of complement so as to finally have two units of free complement present, and the whole test should be repeated anew.

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## PALMAR SYPHILIDES

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THE subject of palmar syphilides should be of general interest on account of the frequent difficulty in diagnosis and treatment, and from the fact that they occur on an exposed part of the body. Every physician must, at some time, be called upon to give an opinion of a palmar eruption which may be the only symptom of a syphilitic infection.

The manifestations of syphilis affecting the palms are sharply divided into those which occur early, and those which occur late in the disease. While there is absolutely no hard and fast line between the so-called secondary and tertiary lesions of syphilis, it is convenient to use the term early syphilides for those usually occurring in the first year of the disease, and late syphilides, for those occurring subsequently. An intermediate or so-called late secondary stage is often included, but it seems unnecessary to do so.

The early palmar syphilides are generally described as being papular, although owing to the thickness of the horny layer of the palms, the lesions are really macular and not elevated as a rule (Figs. 1 and 2). They generally occur simultaneously with lenticular papules upon other regions of the body, though they may occur independently of such lesions. They appear as dull red, pea to bean sized discrete spots, scattered over the palms and palmar surfaces of the fingers; and unless very few in number, are invariably present upon both palms. This is a differential point of great importance as the late manifestations generally occur upon one palm or sole. It should be here stated that whatever is said concerning eruptions of the palms, applies equally to those occurring upon the soles.

The early palmar syphilides soon exhibit a tendency to scale, and then present a picture (Fig. 2) which is not simulated by any other disease with which I am familiar. When, however, the early papular syphilide is confined to the palms alone and shows no scaling (Fig. 1) it may be mistaken for an unusual type of erythema multiforme;



Fig. 1.—Papular syphilide, non-scaling.



Fig. 2.—Papular syphilide, with marked scaling.





Fig. 3.—Circinate squamous syphilide.



Fig. 4.—Circinate squamous syphilide.





a fact that does not seem to be generally recognized. Erythema multiforme occasionally appears in the form of discrete macular lesions upon the palms, associated with bullous lesions of the mouth, and then presents an appearance which the average physician, and not a few dermatologists, could mistake for syphilis.

Two cases of this kind have lately come under my observation. One of these was a young married woman, thirty years of age. She gave a history of having had four or five attacks of "blisters" of the lips and mucous membrane of the mouth, which had lasted for several weeks. When I saw her, she presented numerous crusted and superficially ulcerated lesions of the lips, tongue, and buccal mucous membrane, and a discrete macular eruption confined to both palms, the duration of the attack being one week. An experienced colleague, who had previously seen her, had evidently considered the lesions of the mouth to be mucous patches, as he made a positive diagnosis of syphilis. The absence of other signs or symptoms of syphilis, the history of recurring attacks, and a negative Wassermann reaction made it possible to relieve the patient's consternation, and assure her that she had not been infected with syphilis. A similar case occurred in a patient whom I saw through the courtesy of Dr. Ludwig Oulmann. This was a man thirty-eight years of age who presented, for the third time, an eruption similar to the one above described.

The late palmar syphilides are of special importance as they are apt to be extremely chronic and rebellious to treatment, and often difficult to differentiate from other diseases of the palms. On the palms, as elsewhere, we may encounter an ordinary nodular or a gummous (Fig. 6) syphilide, which may assume a serpiginous tendency, and may or may not ulcerate, according to circumstances. The type of the late palmar syphilide which is of greatest interest is termed the squamous syphilide in the new official nomenclature of the American Dermatological Association, (a classification and nomenclature suggested by my father, Dr. George Henry Fox).

The squamous syphilide is subdivided according to the new classification, into the circinate and the diffuse forms. The circinate type, (Figs. 3 and 4) while not very frequently seen, is, however, absolutely characteristic. The only disease that might possibly be confused with it would be ringworm. In ringworm the circle would be more apt to be complete, the border would be reddish and inflamma-

tory, and numerous tiny vesicles might be observed. At all events, it would not have the flaky scaling, nor persistence that characterizes the circinate squamous syphilide. The diffuse form of the squamous syphilide (Fig. 5) is one that might be called eezematoid. At all events, its chief importance lies in its close resemblance to eezema and also to psoriasis and seborrheic dermatitis (seborrheic eezema). As a matter of fact, it is difficult or impossible to distinguish eezema, psoriasis, and seborrheic dermatitis from each other when they are limited solely to the palms. Even if this were readily possible, it would not be of any practical importance as the treatment of these conditions is similar. What we wish to know is whether the eruption is syphilitic or not. It makes little difference whether it is eezema or psoriasis. As a matter of fact, we are rarely called upon to differentiate syphilis from psoriasis of the palms, as psoriasis very rarely occurs upon this part of the body alone. In almost every case there are psoriatic lesions elsewhere to suggest the nature of the disease. This is not the case with eezema which is often limited entirely to the palms or soles. The type of eezema that simulates the squamous syphilide is the dry, squamous type of the disease.

In considering the differential points, I would say that when the eruption is present upon one palm (is asymmetrical), in nine cases out of ten, it is syphilis; and when it occurs upon both palms, in nine cases out of ten, it is eezema. While eezema may often appear, at first glance, to affect only one of the palmar surfaces, upon more careful inspection a small amount of the disease will generally be observed upon the opposite hand. While the squamous syphilide seems to prefer the center of the palm, eezema is more apt to extend to the palmar surface of the fingers. Another important point is that the borders of the patches in syphilis are more liable to be sharply defined, at times strikingly so, while the patches of eezema are apt to gradually merge with the normal skin. The presence of itching in eezema, and its absence in syphilis of the palms is not of very great importance, as eezema does not exhibit this characteristic tendency upon the palms as it does upon other parts of the body. Finally the diagnosis may be confirmed by the presence of other lesions upon the backs of the hands or elsewhere upon the body. While a positive Wassermann reaction would be of great assistance, it would not, of course, prove that any special lesions were specific. The reaction, is furthermore, negative in a certain proportion of cases, especially



Fig. 5.—Diffuse squamous syphilide.



Fig. 6.—Ulcerating gumma- syphilide.





Fig. 7.—Verrucous syphilide.



Fig. 8.—Verrucous syphilide.



those that occur ten or even twenty years or more after infection.

The great majority of cases of syphilis of the palms and many cases of eczema occur in patches, but, at times, the entire palmar surface of the hand is affected. In a certain number of such cases, there may be a marked verrucous condition (Fig. 8). At times a palmar syphilide may present small discrete horny elevations, called by the French, syphilis cornée (Fig. 7), which may be dug out forcibly with a sharp instrument.

Several other diseases might be mentioned which produce chronic scaly patches upon the palms. Some of these are readily differentiated from the palmar syphilides by the simultaneous occurrence of other lesions upon the body. An example of such a disease is pityriasis rubra pilaris. A verrucous tuberculosis of the palms at times resembles a verrucous syphilide so closely that the differential diagnosis can only be made by the use of the microscope, or a therapeutic test. Hereditary keratosis of the palms would be recognized by the history of its life long occurrence.

Previous to the introduction of salvarsan, the treatment of palmar syphilides was invariably difficult, some cases only disappearing after the most vigorous use of mercury by inunctions or injections. Indeed I have seen cases absolutely refuse to clear up after a long series of salicylate of mercury injections. With salvarsan or allied drugs (neosalvarsan, arsenobenzol, etc.) the treatment is generally recognized to be highly satisfactory and often most brilliant. It is now a common experience to see a palmar syphilide, that may have existed for years, disappear completely in from one to four weeks after a single injection of salvarsan.

#### CONCLUSIONS

1. Palmar syphilides are of importance on account of frequent difficulty in their diagnosis.
2. Erythema multiforme of the palms may simulate the early, non-sealing papular syphilide. When associated with bullous lesions of the mouth, a mistake in diagnosis is very liable to be made.
3. The diffuse form of the late squamous syphilide must be differentiated from eczema.
4. Treatment by salvarsan (or allied drugs) gives brilliant results.

## A SERIES OF RUPTURED AORTIC ANEURYSMS\*

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THE cases which form the basis of this communication form an interesting group because they illustrate the directions which aneurysms may take in relation to other organs. In one case (A-5262) the perforation was external, through the sternum; in one (5444) it was into the superior vena cava; in one (6524) it was into the left pleural cavity by way of the diaphragm; in one (2366) it was retroperitoneal; in one (4719) it was into the left pleural cavity by way of the left lung; in two (5872 and A-8264) it was into the left main bronchus; in one (178202) it was into the left ventricle; and in one (152041) it was into the pulmonary artery; six were therefore aneurysms which sprang from the arch of the aorta. Two were developed from the abdominal aorta.

### CASE I

W. D., Hospital No. A-5262, a negro 43 years of age, was admitted to the Cincinnati General Hospital on August 5, 1916, complaining of "aneurysm."

*Family History.*—Two aunts had died of tuberculosis, otherwise the history was unimportant.

*Past History.*—The patient stated that he had never been sick in bed until about three weeks before admission, when for two weeks he had had pneumonia from which he had recovered very promptly. At the age of seventeen he contracted lues and had a chancre. Also he has had several attacks of gonorrhea. He never had had rheumatism. During the last summer he has coughed a good deal and this symptom has been accompanied by profuse expectoration, and by severe constant and diffuse excruciating pains in the chest, the pain radiated down the right arm. At one time he visited a physician who made a diagnosis of muscular neuralgia and treated him accordingly. He also went to the antituberculosis league clinic and there had chest and sputum examinations, the result of which is not known, except that the physician said that the cardiac rhythm was irregular. At this time there was no external bulging or tumor mass on the chest wall. The

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patient has never complained of dysphagia, aphonia, or defect of vision. He has had no swelling of the legs.

*Present Illness.*—In March, 1915, the patient carried a large roll of wall paper (weighing 250 pounds, he said) on his right shoulder for about a mile. The same evening he noticed soreness in the right chest and shoulder. The soreness became pain, and persisted for the next ten months. In January, 1916, he noticed a tumor mass about the size of a hen's egg on the right side of the chest. Hot applications were made to this, and it seemed to become smaller. On February 10, 1916, the patient papered a room but was forced by the pain to discontinue further work. Since that time he has been confined to bed. During this period of confinement the tumor mass progressively increased in size. On July 28th there was a severe hemorrhage from the tumor mass, and two days later another. Since then the mass has decreased in size. During the first hemorrhage there was no pain; during the second, pain was severe, especially just before it began. Since then there has been no pain.

*Present Condition.*—The patient was a black, intelligent, well nourished and well-developed man. The eyes were normal. The posterior cervical glands were palpable on both sides. The teeth were in fairly good condition, but the gums were pyorrheic. In the right pectoral region was a large smooth pulsating mass bounded above by the clavicle, below by the sixth rib, externally by the axillary fold, and internally, it extended 1.5 inches to the left of the sternum. At a point corresponding to the junction of the third costal cartilage and the right border of the sternum there was a circular opening about  $\frac{3}{4}$  of an inch in diameter from which blood oozed in small amount. Palpation showed that the mass was fairly and generally firm. Over it there was a slight systolic thrill, and an indistinct diastolic shock. A tracheal tug was present. Both radial and femoral pulses were regular, and synchronous. No systolic murmur was heard over the trachea. Over the right lung tactile and vocal fremitus were increased. Resonance was decreased anteriorly in the sixth intercostal space. The breath sounds were harsh over the whole left lung, especially at the base posteriorly. The apex of the heart was in the sixth intercostal space one inch outside the nipple line. Nothing unusual was discovered in examination of the abdomen. Upon the back, especially on the right side were numerous macules. The urine contained no casts, sugar, or albumen, and was clear, acid, and had a specific gravity of 1018. The blood pressure was 115 systolic, 80 diastolic.

On August 14th, a sudden hemorrhage from the opening in the thoracic tumor mass occurred, during which the patient became cyanotic and pulseless, and had rapid, gasping respirations. Death occurred half an hour later.

The clinical diagnosis was *aneurysm of the aorta rupturing externally*.

#### AUTOPSY PROTOCOL

The body was that of a well developed, muscular negro, apparently 40 years of age. Rigidity was present, but posterior lividity was absent. The pupils were small and equal, and in each cornea was an early arcus senilis. The teeth were in fair condition, but the somewhat retracted gums were pyorrheic. The peripheral lymph glands were palpable.

Upon the chest there was a rounded, smooth, fluctuating mass that began at the left clavicle and extended downward to the level of the third rib. To the left it reached 3 cm. from the midsternal line, and to the right 7 cm. from the midsternal line. It measured 11x10 cm. in diameter. Near its lower border was an opening, 7 mm. in diameter, with indurated edges, from which blood oozed. The chest was well developed and proportioned, and the costal angle was obtuse. The abdomen was flat. The right pectoral muscles and surrounding tissues were infiltrated with blood and at frequent points there were organizing clots. The second right costal cartilage and adjacent portion of the sternum were eroded.

In both pleural cavities there were widespread fibrous adhesions. The pericardial cavity was obliterated by old fibrous adhesions. The heart itself was pale and flabby. The valves were not evidently abnormal, except possibly the mitral the edges of whose cusps were somewhat thickened. The myocardium was pale and cloudy and not evidently fibrotic. The aorta, beginning just above the sinuses of Valsalva, was enormously dilated, especially anteriorly and to the left, and just beneath the eroded sternum the dilatation was more localized and here there was a sac about the size of a hen's egg which had become adherent to the sternum. From this cavity an opening 3 cm. in diameter led into the pectoral tumor mass. The aneurysmal sac contained organized clots. The diffuse dilatation involved the whole ascending arch to the origin of the great vessels which were not involved. Nevertheless the whole internal wall of the aorta was thickened and roughened by the presence of numerous subintimal patches of evidently fibroid plaques, in some of which there were evident degenerative changes.

In none of the other organs were there essential changes except in the kidneys which were moderately fibrotic and upon which the capsules were adherent.

The *anatomic diagnosis* was aortic dilatation; aortic aneurysm perforating externally through the sternum; luetic mesaortitis; chronic diffuse nephritis; obliteration of the pericardial cavity; hemorrhage.

#### REMARKS

In this case the first symptoms, cough and pain, appeared 25 years after the appearance of the primary lesion, and also it appeared suddenly after exertion. The history suggests that the strain of carrying a heavy weight was the factor which overcame the resistance of the aortic wall and caused it suddenly to bulge.

#### CASE II

T. B., Hospital No. 5444, a white man, aged forty-three, married, was admitted to the hospital complaining of dyspnea on exertion, cough, and dizziness.

His family history was negative.

*Past History.*—He contracted gonorrhea twenty years ago. About a week later he noticed sores on the legs. He denies luetic infection. His wife is living and well; she has had one miscarriage. Two children died in infancy. The patient has drunk alcohol to excess for many years. For the last six months he has had to get up twice each night to urinate.

*Present Illness.*—Two weeks before admission, the patient complained of sore throat, and he began to cough. The following day he felt worse, and the throat became swollen. He could not button his collar, and it became difficult for him to breathe. The throat has continued to swell the last few days, and his condition has gradually grown worse.

*Present State.*—On admission to the hospital the patient's general condition was fairly good. The pupils were inactive to light. The right pupil was pin-point in size, the left one was larger and irregular. There was marked pyorrhea. The neck was swollen. The lungs were negative, except for a few fine crepitant râles in the lower axilla on each side. The heart apex was not visible. The rhythm was regular. There was a systolic murmur at the apex, transmitted to the aortic area. The second aortic sound was metallic and accentuated. Pulses were synchronous, the left larger than the right. Blood pressure, right arm, systolic 130, diastolic 60, pulse pressure 70. Left arm, systolic 115, diastolic 50, pulse pressure 65. The abdomen showed marked distention but no rigidity. The liver was palpable three finger-breadths below the costal margin. No masses were felt. Knee jerks were not obtained. There were old scars on lower third of each tibia. An x-ray plate of the chest showed diffuse broadening of the upper mediastinum, suggesting diffuse dilatation of the arch of the aorta. The patient had 3,800,000 red cells, hemoglobin 70 per cent, and 7,800 leucocytes. A differential count showed 20 per cent lymphocytes; 21 per cent large mononuclears; 4 per cent transitionals; and 55 per cent polynuclear neutrophils. There was capillary venous congestion of the chest wall and back. Laryngologic examination was attempted, but owing to the swelling of the tissues of the mouth and pharynx it could not be made.

The patient developed delirium tremens. His condition gradually grew worse, and he died eleven days after admission. On the two days preceding death there were signs suggesting consolidation of the lung at the right base posteriorly.

*Hospital Diagnosis.*—Dilatation of aorta, mitral insufficiency, chronic alcoholism, lobar pneumonia.

Diagnosis from history (R. S. M.) Aneurysm of arch of aorta; mediastinal tumor; pneumonia of right lower lobe; syphilis; general paresis; arteriosclerosis; chronic alcoholism.

The history and physical findings together with the x-ray examination point conclusively to a mass in the mediastinum. The swelling of the neck together with the engorgement of the veins of the upper half of the body suggest pressure on the superior vena cava. Such signs are commoner in connection with malignant growths in the mediastinum than with aneurysm. In this patient, however, although the patient denies luetic infection, and, in spite of the fact that a Wassermann test was not made, the evidence of a past luetic infection seems conclusive. The scars on the shins, the changes in the pupils, the absence of knee jerks, the differential count, all seem to point conclusively to syphilis. These factors in conjunction with the duration of symptoms, would seem to favor a diagnosis of aneurysm of the aorta rather than neoplasm. (R. S. M.)

## AUTOPSY PROTOCOL

The body was that of an adult white man of about forty-five years, and five feet seven inches in height. At first sight there was an appearance of swelling of the neck and lower half of the face, but there was no pitting on pressure, and no evidence that there was anything but a fatty accumulation. The whole appearance of the body gave the impression of a *typus femininus*. The pubic hair was limited to the pubic triangle, and there were but a few scattered hairs on the thorax; otherwise the trunk was bare. The hair of the head was scanty as was that of the face. The body was warm. The neck and sides of the head, the shoulders and upper part of the thorax were livid, as was the whole dorsal surface of the body. There were a very few petechial congestions upon the chest, which disappeared on pressure only to return. Rigor mortis was absent, the pupils were equal; the teeth distinctly bad, both carious and pyorrheic. There was the wound made for intravenous medication in the bend of the elbow. The legs showed, upon their median thirds, the copper or ham-colored sears of old luetic lesions, covered with smooth shiny skin. The testicles were apparently atrophic. There was a moderate phimosis but no preputial sears.

When the body was opened, the lungs did not collapse. The right was somewhat compressed by a very considerable hydrops, the fluid of which was clear. The liver reached 11 cm. below the sternum, its edges were thick and rounded. The omentum was adherent in the left inguinal region and in the region of the spleen. The left lung was adherent at the apex by a broad band of old fibrous adhesions, and by less extensive ones to the diaphragm. It showed no evidence of inflammation or consolidation. The surface was smooth and not especially congested. On section nothing but a moderate edema could be disclosed. The right lung was partially collapsed and was adherent only at the apex by fibrous adhesions. In this organ there was no superficial evidence of inflammation or consolidation except on the diaphragmatic surface near the lateral edge of the lower lobe, where there were three or four small nodules in the atelectatic substance, which upon section seemed to contain, each of them, a small drop of purulent exudate. Section of the whole lung showed only moderate edema with very little congestion. The bronchi were much congested.

The heart, cervical and oral organs were removed together. There were no obvious lesions in any except the heart and lower part of the trachea. The tongue was normal, the tonsils atrophic and healthy, and the esophagus, larynx, and pharynx normal. The trachea, like the main bronchi, was tremendously congested. The thyroid was apparently normal. The cervical lymph glands were succulent and pale; the aortic and bronchial glands were pigmented and juicy. There was no vestige of thymus.

The heart was large, both hypertrophied and dilated. The dilatation was chiefly evident in the right side. The right auricle was extremely dilated. It contained no clots. When the inferior cava and superior cava were joined by incision, and the superior cava opened, a little mass of blood clot appeared 5 cm. above the foramen ovale. When this was removed, a small opening in the wall of the vein was exposed 0.5 cm. in diameter, which passed into a cavity between

the aorta and the superior cava. Near the opening and below it were two small patches, 2 to 3 mm. in diameter, which were softened, and there were partially softened areas in the caval wall where perforations were incipient. When the aorta was opened, the mouth of an aneurysmal sac 1 cm. in diameter was found 4 cm. above the junction of the left and posterior aortic cusps. The sac, which was not opened, was filled with blood clot, and through this mass a probe could be passed out the opening in the cava. The aorta itself was generally dilated in its ascending and transverse parts. The walls were affected by a generalized sclerosis, which extended into the great vessels of the neck. The appearances were typical of a luetic mesaortitis. In the region about the aneurysmal opening and the openings of the great vessels, were six small incomplete aneurysms. None of these were larger than the tip of the little finger.

The spleen was small and not obviously abnormal.

The liver was very large and swollen. Its generally brownish surface was mottled thickly with yellow, and scattered here and there under the capsule were a few small round, fairly solid bodies of about half a millimeter in diameter. The organ cut with a slight increase in resistance. The cut surface showed no evidence of cirrhosis, though the friability was decreased. The cut surface was quite generally yellow, with congested areas.

The kidneys were of about normal size. The capsules stripped with ease, leaving rather pale surfaces with no markings of congestion, and with a number of depressed infarct scars. The cortices were very slightly decreased in thickness. The lines of demarcation between cortex and medulla were normally evident. The pelves of the kidneys, the ureters, and bladder seemed normal. The testicles were small and, macroscopically, showed nothing abnormal. The adrenals, embedded in masses of fat, were apparently smaller than normal.

The stomach and small intestines, and, to a less extent, the large, were generally congested and the mucosa was covered with a tenacious layer of mucus.

The brain was examined. After the calvarium had been removed, it was evident that the dura was profoundly modified upon both lateral aspects. Over the left temporo-frontal region and running up toward the vertex, the dura was thickened and much pigmented upon its inner surface. In the right temporal and parietal region the dura was apparently formed of two layers, between which there were two large communicating pouches filled with degenerating blood. These were so large that they had compressed the cortex to a considerable degree, and the depressions so formed were best marked immediately in front of and behind the Sylvian fissure. The inner walls of these spaces were brown and as thick as a normal dura. Beneath these areas upon each side, the pia was much thickened and opalescent.

In the mesentery was a large lipoma. Cultures made from the heart's blood were negative.

The *anatomic diagnosis* was luetic mesaortitis; aortic aneurysm perforating into the superior vena cava; multiple incomplete aortic aneurysms; cardiac hypertrophy and dilatation; myocardial fibrosis; pachymeningitis interna hemorrhagica; right pleural effusion; enlarged fatty liver; mesenteric lipoma; typus femininus.

## REMARKS

In connection with these anatomic findings, it is only necessary to remark that the aneurysm perforating into the superior vena cava is an exceedingly rare condition, and that the perforation was a recent one, as shown by the fact that the edges of the opening were ragged and not healed. The pachymeningitis was an interesting, but not a rare condition, though in this case it was very well developed and almost completely unilateral. The atrophic testicles showed, upon examination of sections, that the interstitial cells of Leydig were almost completely absent, and this, one suspects, was the basis of the feminine type of body, inasmuch as it is believed that the interstitial cells form the tissue which has to do with the development of the secondary sex characteristics.

In this case lues was denied, but gonorrhea, acquired twenty-three years before the first symptoms, cough and sore throat, was admitted.

## CASE III

C. S., Hospital No. 6524, a negro, 35 years old, was admitted to the Cincinnati General Hospital on December 9, 1915, complaining of swelling of the abdomen.

*Family History.*—Negative except that his mother died at the age of 52. She had had a hemiplegia since the age of 42.

*Past History.*—He had had "typhoid malaria" at the age of 9, at which time he was ill 5 months. At 18 he had gonorrhea and syphilis. For these he was not treated, but for a short time took an "herb medicine." At the same time he had an inguinal bubo which broke down.

*Present Illness.*—For a year he had felt a weakness in the left side along the mid-axillary line. Five months before admission, while working, he felt a sharp pain in the side and had to stop work. Two weeks later he returned to work wearing an abdominal support. He gradually became weak and six weeks before admission, took to his bed. In the last two weeks he had several attacks of severe abdominal pain which he described as a constant ache. At the time of admission, he complained of distention without pain. He had no appetite, was constipated, and had lost 35 pounds in weight. He had no night sweats and no dyspnea.

*Present Condition.*—He was emaciated and had a rather worried pained expression. The pupils were equal and reacted to light and during accommodation. The teeth were poor and the gums were pyorrheic. The tonsils were hypertrophied. The cervical glands were palpable. He was unable to sit erect in bed without support. There was visible pulsation in the second left interspace anteriorly, and just opposite the 12th dorsal and first lumbar vertebræ was a pulsating, expansile mass about the size of a hen's egg. This mass was painful on pressure, and the adjacent muscles were tense.

Examination of the lungs showed a flat percussion note over the apex posteriorly, below which the note was resonant, becoming flat at the base and over the expansile mass. There was also apical dullness and impaired basal dullness on the right. Anteriorly there was slight impaired resonance below the clavicle on the left, and, on the right, apical impairment and lower axillary dullness. Auscultation showed, posteriorly, tubular distant breathing at the left apex, roughened over the scapula, with no râles or friction sounds; roughened inspiration, and prolonged expirations on the right. Anteriorly the sounds were rather distant on the left; on the right, the roughened sounds had a tubular quality. In the axillæ the sounds were normally vesicular. Vocal fremitus was present and equal on the two sides.

The apex of the heart was in the fifth space within the mammillary line. Percussion of the cardiac area showed:

	LEFT	RIGHT
1st interspace	5 cm.	3.7 cm.
2nd "	6 "	4.0 "
3rd "	7.5 "	4.5 "
4th "	8.5 "	4.4 "
5th "	9.5 "	4.0 "
6th "	10.0 "	
	Apex 6 "	

The abdomen was slightly distended, especially in the lower left quadrant where the skin was scaling from a previous local application. Also the abdomen was tense and rigid. The inguinal glands were enlarged. There was a left inguinal hernia, and the right inguinal ring was wide. The entire left side of the abdomen and the posterior muscles were rigid, and on the left there was tenderness which caused the patient much pain when sitting. No bruit was heard over the mass in the back. There was no edema. The knee kicks were present and the Babinski sign was absent.

The urine was normal. Sp.gr. 1016; no sugar; no albumin. The blood pressure was systolic 124, diastolic 92.

Later (Dec. 15) the aortic second sound was accentuated, and an x-ray plate disclosed erosions of the 12th rib and vertebra. On Dec. 16th a note was made that a "bruit and pulsation was felt on deep pressure at the base of the xiphoid, to the left." The Wassermann reaction was clearly positive. The hemoglobin was 65 per cent, and the leucocyte count was 8,200.

There was no further change noted until death.

The *clinical diagnosis* was, aneurysm of the abdominal aorta causing erosion of the 12th rib and 12th dorsal vertebra; pulmonary tuberculosis in the second stage; chronic nephritis; hypostatic pulmonary congestion; arteriosclerosis; internal hemorrhage from rupture of the aneurism.

#### POSTMORTEM PROTOCOL

The body was that of a slenderly built, somewhat emaciated adult negro between 30 and 40 years of age. The hair and beard were streaked with gray. There was no peripheral edema. The peripheral lymph glands were not noticeably en-

larged. The pupils were equal. The whole body seemed exceedingly anemic. The beds of the nails were colorless. Rigor mortis was present. Lividity was not evident.

When the body was opened, there was a gush of blood from the left pleural cavity (1250 c.c.). There was no fluid in the abdominal cavity, and there were no intestinal anomalies or abnormalities. The appendix was normal, and very long. After the serum in the left pleura had been syphoned off, a very large blood clot remained, and a small (165 grams) pale compressed lung. It appeared that the blood had come from an opening through the diaphragm, close to the vertebræ, just below and to the left of the esophagus. The opening led into a large cavity filled with blood clots that extended extraperitoneally to the brim of the pelvis on the left, and which also extended to the right just below the kidney. On the left the aneurysmal sac was very large and had exerted pressure upon the renal vessels so that the blood supply of the left kidney had been reduced to a point where the kidney was almost the clear white of exceeding anemia. The bodies of the 11th and 12th dorsal, and of the 1st and 2nd lumbar vertebræ were eroded, leaving the cartilages unaffected. The left 12th rib was completely eroded for about an inch near its attachment. The aortic opening of the aneurysm was on the posterior surface of the vessel immediately above the renals and just opposite the celiac axis. It measured 3.5 cm. longitudinally and was 1.5 wide. The margins of the opening were thickened and hyaline in appearance and typically luetic.

The left lung was very small, contracted, pale, and crepitant throughout. There were no pleural adhesions. The right lung (343 grams) was normal in every macroscopic respect. The liver (1520 grams) was pale and showed nothing abnormal. The spleen (110 grams) was very soft, almost fluid, and was adherent to the diaphragm. The Malpighian corpuscles could not be seen. The left kidney (170 grams) was almost white in color. The capsule removed with extreme ease, leaving a very pale, moist surface studded with numerous very small petechial hemorrhages. The right kidney (180 grams) was larger. It was moist and the surface beneath the easily removed capsule was flecked with small hemorrhages. The whole organ was of the mottled type. The cortex was somewhat thicker than normal, and on its cut surface could be seen congested interlobular vessels and congested glomeruli. The line of demarcation between cortex and medulla was distinct.

The heart (235 grams) was contracted. There were no valvular defects. The myocardium seemed healthy except for pallor. The coronaries were not sclerosed.

*Anatomic Diagnosis.*—Left hemothorax; aneurysm of the abdominal aorta which had perforated into the left pleural cavity through the diaphragm; erosion of the 11th and 12th dorsal and 1st and 2nd lumbar vertebræ, and of the twelfth rib (left); luetic mesaortitis; subacute diffuse nephritis; anemia.

#### REMARKS

In this case lues was acquired 16 years before the first symptom, which in this instance was pain in the side. Later abdominal pain also appeared.



## CASE IV

A. D., Hospital No. 2366, a colored woman, 27 years old, was admitted to the Cincinnati General Hospital on June 6, 1915, complaining of pain in the left side of the abdomen, pain in both legs, and inability to walk.

The *family history* was given in the clinical records as irrelevant.

In the *past history* there was a note of the ordinary diseases of childhood. Venereal disease was denied, as also was the use of drugs or alcohol. The appetite had been poor and the movements of the bowels irregular.

The *present illness* began, seven months before admission, with a sharp pain in the back low down on the left side. Soon after that, the pain shot down the left leg. At various times since the first attack of pain, a swelling would appear in the left iliac region. This would remain for a few days, and then as it decreased in size the whole left leg would swell. For the last month this swelling has been persistent and the pain has been worse.

The *condition at the time of admission* was given as follows: General condition fair; tongue coated; teeth in bad condition. The apex beat of the heart was localized; the cardiac rhythm was regular, the sounds weak; the pulses equal and regular. Upon the left side of the abdomen in the iliac region was a mass, over which there was tenderness and rigidity. The right leg and thigh were swollen. The uterus was deflected to the right, and there was pain in the fornix.

A later note (June 16) called attention to the fact that the left iliac mass had increased in size and that there was associated with it expansile pulsation and a bruit. A Wassermann reaction was positive. Later (June 18) a left submaxillary enlargement was noted, with glossitis. Ten days later the pulse was very weak and becoming rapid. Pain in the abdomen and left leg were troublesome. There was edema of the left leg and some edema of the tissues of the back in the lumbar region. Partial ankylosis of the left knee and hip were suggested. Two days later, shortly after midnight, the patient seemed almost collapsed. She was pulseless and unconscious; the heart action was fairly good; the respirations were quiet and decreased in number. She rallied for a time and then at 5 A. M. she suffered a second collapse. The mass which had been larger subsided and an emergency operation was evidently unsuccessful though no more notes appeared in the history.

*Clinical Diagnosis.*—Ruptured sacculated aneurysm of the left common iliac involving the internal and external iliaes; syphilis.

## POSTMORTEM PROTOCOL

The body was that of an emaciated and anemic young adult colored woman. The left leg was rotated externally and abducted to an angle of about 30° as the body lay upon the table. The right leg was abducted to a less extent. Both legs were edematous, the left more than the right. The skin and conjunctivæ were pale; the pupils slightly and equally dilated. Upon the lower leg over the middle of the tibia (left) was a large contracted, pigmented, atrophic, smooth scar, 5 cm. in diameter. Upon the upper part of the thigh anteriorly and laterally were a few sluggish, rather irregular, crusted ulcers of varying sizes, the edges

of which were sclerotic and fibroid. In the abdominal wall in the midline was a recent unhealed incision which ran from the umbilicus to the pubis. The edges were approximated by silk worm gut (cutaneous) and catgut (muscles) sutures, between which oozed a sanguinous fluid.

Upon opening the body, it was found that the tissues were generally extremely anemic and rather moist and edematous. The organs in the abdominal cavity held relatively normal positions. The transverse colon was V-shaped; the splenic flexure formed a sharp inverted V. The appendix was small but apparently not abnormal. To the left of the midline, just internal to the attachments of the sigmoid was a ragged opening leading into the subperitoneum, which was filled with a mass of blood clot, which was in part very friable, in part very tenacious. This extraperitoneal sac ran up behind the kidney to the diaphragm, and down below Poupart's ligament, and had a total length of 37 cm. It also extended to the right of the midline where its floor was formed of the psoas and iliac muscles. Along the left border of this ran the iliac vessels, and above it ran the ureter, which apparently was not affected. The opening from the abdominal aorta was posterior and measured 8 by 4 cm. Its lower end occupied the former situation of the bifurcation of the aorta, and the dilatation had included the left common iliac. The opening of the right common iliac was in the wall of the sac. The margins of the opening were thickened, rounded, and sclerotic. The four lower lumbar vertebrae, on their left sides and anterior faces, were eroded. Upon the body of the 5th was an exostosis about 15 mm. high and 7.5 mm. thick. The body of the 4th was especially damaged, to the extent of eroding almost one-fourth of the body of the bone. The transverse processes of the 3rd and 4th vertebrae were almost completely eroded, only a few fragments remaining, and between these the sac of the aneurysm had penetrated until it had reached the skin posteriorly. On the left side, the sigmoid was closely adherent to the sac, and above, the kidney, spleen, and diaphragm, were also adherent. The irritative process had involved the diaphragm so that the lower left lobe was closely adherent to the midriff immediately opposite the sac.

The lungs were free, and upon opening the thorax, partially contracted. Both were exceedingly pale and air-containing. They held but little blood or fluid, except at occasional points in the dependent portions where there were localized congestions. The heart was small, atrophic, and very pale. There were no remarkable lesions observable in any part. The valves were healthy and the endocardium smooth. The aorta (ascending and arch) exhibited a few patches of only moderate sclerosis and fatty degeneration, but there were no evidences of atheroma or hyperplasia of the intima. In these respects it differed entirely from the abdominal aorta in which there was a diffuse and intense syphilitic atherosclerosis in all stages of development. The kidneys were somewhat enlarged; from both the capsules were readily removed. The right was somewhat congested; the left was exceedingly pale. The left was adherent to the false aneurysmal sac. In the right, the glomeruli were congested, and the cortex marked with dilated vessels. In both, the cortices were thickened. The pelves and ureters were not abnormal. The liver was exceedingly pale and yellow. Upon its surface were numerous adhesions which ran to the diaphragm and to the transverse

colon. In its substance were a few small areas, one of them 20 mm. in diameter, hyaline in appearance, and with evidently softened or caseous centers, resembling, to a certain extent, gummas. The portal connective tissue was somewhat hyperplastic. The spleen which was adherent on all sides by old firm adhesions, was somewhat soft, friable, cloudy, and succulent. The Malpighian follicles were enlarged. The peribronchial lymph glands were congested and moist, and several of them contained what seemed to be small abscesses holding a rather mucoid greenish purulent material. The mesenteric lymph glands were pale and juicy. The genitals showed no abnormalities. The brain was merely pale and edematous. The pituitary and pineal were not apparently abnormal.

*Anatomic Diagnosis.*—Ruptured (extraperitoneal) abdominal aneurysm; syphilitic aortic atherosclerosis; erosion of lumbar vertebræ; acute peribronchial lymphadenitis; acute diffuse nephritis; ulcerative dermatitis; hepatic gummas; general anemia.

#### REMARKS

In this case lues was denied nor was there any history of venereal disease. The onset occurred at the age of 26 and was characterized by pain in the left side shooting down the leg.

#### CASE V

W. C., Hospital No. 4719, a colored man 42 years old, was admitted to the Cincinnati General Hospital on Nov. 9, 1915, complaining of bleeding from the mouth after coughing; pain on the left side of the chest; a "tight feeling" in the chest, and roaring in the ears.

*Family History.*—Negative.

*Past History.*—The patient contracted syphilis in 1899. For this he was treated for 3 months in the Cincinnati Hospital. He also took a proprietary medicine (S. S. S.) for three years. Between the ages of 18 and 26 he performed in a circus, breaking a strap buckled around his chest by expanding his chest. He had always been apparently strong and well.

*Present Illness.*—On July 5, 1915, he began to have burning pain in the left chest. He felt as though some one had struck him. The pain was also sharp and ran down the left arm to five inches below the elbow. Often he has had to lie down to get relief. At night he lies on his stomach to relieve the pain. His discomfort is less when he is at work (odd jobs). Some time before admission he had an attack of dyspnea with cough, and in this attack he spat up about two tablespoonfuls of clotted blood. Previous to this he had never been dyspneic nor had he had a cough. He said he had had night sweats off and on for 10 years, especially in winter. He had been taking two glasses of beer daily, and whiskey once a week.

*Present Condition.*—The general condition was good, though the teeth were bad. The chest was well formed and expansion was good. The supraclavicular spaces were somewhat retracted.

The right lung was negative except that the breath sounds were harsh pos-

teriorly. The left lung was dull over the upper lobe anteriorly, and over the upper lobe there was bronchial breathing. The apex of the heart was not located. There was dullness 1 cm. to the right of the midsternal line in the first interspace. (The left border was not noted.) The cardiac rhythm was good, the sounds were clear and no murmurs were heard. The abdomen was negative. Blood pressure, right arm, systolic 112; diastolic 66; pulse pressure 46. Left arm, systolic 118; diastolic 70; pulse pressure 48. The urine showed no albumin and no sugar. On July 26th, the patient coughed and spat out about a teaspoonful of blood. The following day the urine was reported to contain a little bile. On August 31st, the urine contained a heavy ring of albumin, and hyaline and granular casts.

On Sept. 5th, the patient seemed to be improved, though he still expectorated blood. The urine was free from albumin. On Sept. 9th, he left the hospital but returned six days later. On Oct. 1st, he had a small hemorrhage, apparently from the lungs, at which time 2 ounces of blood were lost. By Nov. 14th the patient was complaining of considerable pain, his pulse was described as bad, and hemoptysis was persistent. On Nov. 15th he had a paroxysm of intense pain; at 9 A. M., the pulse became very weak and he died an hour later.

During his stay in the hospital, the patient's temperature was slightly elevated. The elevations reached 101° F. daily during the early part of September, after which the variations ranged between 98° and 99.5° and 101°. The pulse curve followed that of the temperature.

On October 11th, the blood count showed 15,750 leucocytes, of which 79% were polynuclear, 2% large mononuclears, 10% lymphocytes, and 9% transitionals. A Wassermann reaction was strongly positive. No tubercle bacilli were found in the sputum.

*Clinical Diagnosis.*—Aortic aneurysm.

#### POSTMORTEM PROTOCOL

At the time of the postmortem, the body was warm; rigor mortis was not present, and posterior lividity was faint. The body was that of a splendidly formed, well nourished, powerful, olive-skinned man in the prime of life. He seemed to be not more than 30 years of age. Upon the skin there were no blemishes except rather numerous small atrophic scars upon the legs below the knees. There was a very slight edema over the tibiae above the ankles.

The thorax was unusually well developed, and powerfully muscled, but it seemed to be somewhat fuller on the left side. Percussion gave an absolutely flat note.

When the ribs were incised, there was a bloody oozing from the line on the left. When the sternum was removed, the right lung was partially and incompletely collapsed. When the abdomen was opened, there was nothing abnormal noted except in the region of the diaphragm, which, on the left, reached to the 8th interspace in the mammillary line and to the 10th rib in the axillary. On the right side it reached to the lower border of the 7th rib. The diaphragm on the left side was forced down in the form of a semispherical prominence into the abdominal cavity, and palpation of this dome-shaped mass indicated the presence of fluid or semifluid contents within the pleural cavity or at least above the diaphragm. Later, dissection showed that the left pleural cavity was completely filled with

a tremendous amount (not measured) of semifluid clotting blood, and that the left lung was adherent to the diaphragm and to the parietes above one of the upper lobes. In the region of the usual position of the left lung, including the area usually filled by the lower part of the upper and upper part of the lower lobe, was a rounded mass which on section appeared to be the huge sac of an aneurysm filled with blood clot and covered with atelectatic lung substance. It appeared that the connection between the aorta and the sac was in the transverse arch just to the right of the origin of the right subclavian, which, in this case, was not a branch of the innominate. The entrance to the sac was a rectangular one, measuring about 2.5 by 1.5 cm. The margins of the opening were thickened and sclerosed. The sac had apparently projected toward the left lung, which it had finally penetrated and into which it had ruptured, for the aneurysmal wall extended not more than a third of the distance about the sac, which was as large as the head of a normal fetus at term. The lung tissue was compressed about the sac and completely atelectatic and also contained much bloody infiltration. The perforation had occurred lateroposteriorly in the thickened fibrous wall of the upper lobe. In the neighborhood of the perforation were several places at which perforation was evidently incipient. The aorta was diffusely affected by a typical luetic mesaortitis, and in the descending arch were two patches at which the aortic wall was thinned and hyaline in appearance and slightly bulged. The main branches of the aorta were all thickened and sclerotic. The right lung showed nothing more than a moderate edema. It was air-containing throughout and had no areas of consolidation. It was adherent to the diaphragm beneath the lung, and in this region there were several masses that had every appearance of cartilage. They were clear, bluish white and opalescent, and were embedded in the diaphragm. They resembled sesamoid bones. The liver was ptotic, to the extent that immediately the body was opened, at least half of the right side of the diaphragm could be seen. The lower edge reached 11 cm. below the costal border in the mammillary line and 15 cm. below the ensiform. It was large (2220 gm.) and pale and showed no gross lesions. The kidneys were enlarged (left 175 gm., right 180 gm.) and pale. They were edematous and showed no evidence of sclerosis or gross change. The spleen was (225 gm.), juicy, friable, and pale. The follicles were not visible. The brain was not removed.

The heart was small and contracted. There were no gross valvular defects. The aortic valves were not sclerotic. The coronaries were apparently healthy. The muscle was perhaps somewhat fibrotic in the papillary regions. The walls of the left ventricle were thickened.

*Anatomic Diagnosis.*—Diffuse aortic luetic mesaortitis; aortic aneurysm (transverse arch) ruptured into the left pleural cavity; pleural and pericardial adhesions; incomplete aneurysms of descending arch of the aorta; pulmonary atelectasis (left); hemothorax (left) cartilaginous bodies in the diaphragm.

#### REMARKS

Lues was acquired, in this case, 16 years before the onset of the essential symptom which was pain in the chest running down the arm.

## CASE VI

J. M., Hospital No. 5872, a negro 37 years old, was admitted to the Cincinnati General Hospital on November 11, 1915, complaining of cough, dyspnea and weakness.

*Family History.*—Negative.

*Past History.*—When he was 21 years old he had rheumatism. In 1910 he had night sweats for three weeks but without cough. Since that time he has had occasional night sweats. He had gonorrhea ten years ago, but denied lues. Until 1908 he was a heavy drinker, but since that time he has not used alcohol. In June, 1915, he experienced for the first time asthmatic attacks, and dyspnea on slight exertion. He had severe pain in the back in May, 1915. His feet have never swelled.

*Present Illness.*—On November 10th, the patient began to cough and feel weak and dyspneic. He complained of severe pain over the heart. On November 11th his sputum was bloodtinged. He had no sweats or chills. His feet were swollen slightly on admission.

*Present Condition.*—The general physical condition was poor; there was a decided pyorrhea. The throat was congested. The chest showed diminished expansion on the left, posteriorly. The percussion note was hyperresonant on the right generally, except at the apex where the note was normal, and anteriorly to the fifth interspace where the note was dull. Auscultation revealed râles of all kinds with bronchovesicular breathing throughout the right side. On the left there was bronchial breathing over the entire left lung except low down anteriorly. Râles of all sorts were heard generally. Vocal fremitus was slightly increased on the right, but absent at the left base. The apex of the heart was 12 cm. to the left in the 5th interspace. Relative cardiac dullness extended 6 cm. to the right. The second pulmonic sound was accentuated. The first sound at the apex was accentuated and impure. No murmurs were heard. The rhythm was regular. The arteries were quite hard. The abdomen was markedly distended. Knee jerks were present. Babinski's reflex was normal.

On November 11th, the leucocytes were 13,000, of which 79% were neutrophils, 10% large mononuclears, 8% lymphocytes, and 2% transitionals. The urine showed a trace of albumin, some red blood cells, and leucocytes, but no casts.

On November 13th, the urine showed a faint trace of albumin, and a few hyaline and granular casts. Respiration was difficult. The patient complained of severe abdominal pain and distention. He coughed a good deal, and there was "evidence of fluid in the left side of the chest."

On November 14th, amphoric resonance and breathing were heard over the left front in the second interspace. In the left axilla the note was hyperresonant and the breath sounds though distant were distinguishable. A metallic tinkle was heard at this point. Coin sounds were not heard. In the left back the note was flat between the spine and the scapula, and breath sounds were absent. The left front, except to the second interspace, was flat, the vocal fremitus was increased, and bronchial breathing was heard. On the right side the breath sounds were exaggerated and accompanied by moist and mucous râles. The percussion note

was hyperresonant. An aspirating needle inserted at the angle of the scapula on the left permitted the withdrawal of a few drops of a thick purulent fluid.

On November 15th, there was distinct tubular breathing in the left back above the angle of the scapula. Below this the breath sounds were absent and the percussion note was flat. In the 2nd left interspace in front, there was amphoric resonance and tympany, metallic tinkling, and whispered pectoriloquy. On the right, the resonance was fair and the breath sounds roughened.

On November 16th, an x-ray plate showed the entire left side opaque, suggesting fluid. The right side was fairly clear. The heart was not displaced.

On November 17th, the left back was still flat, but the breath sounds were reappearing, and there was a slight tactile fremitus. The symptoms were improving. At 10 P. M., the patient died very suddenly during a profuse hemorrhage from the lungs. The hemorrhage was estimated at two quarts.

Throughout the patient's stay in the hospital he had a daily fever reaching from 99.8° to 103.8° F. The pulse varied between 95 and 132. The respirations ran between 20 and 40.

*Clinical Diagnosis.*—Moderately advanced pulmonary tuberculosis; (third stage); cavitation of left upper lobe; pleuropneumonia (left posterior); chronic diffuse nephritis; generalized arteriosclerosis.

#### POSTMORTEM PROTOCOL (B)

The body of a well developed and apparently well nourished colored male adult about 30 years of age. On inspection, clotted blood was noted around nose and mouth. The pupils were contracted and the eyes were slightly bulging. The teeth were in a fair condition, although several were missing. There was a slight distention of the abdomen. The hair on the scalp was scanty. The skin over the entire body appeared dry and frosty. There was a slight superficial wound, with beginning granulated edges, under the crest of the right iliac bone. Marked phimosis was evident. Over both tibia were numerous circular depressed old scars. Postmortem rigidity was present and beginning lividity could be seen posteriorly.

A median incision passed through well nourished thoracic muscles and fat in the abdominal wall. When the abdominal wall was cut, the small intestines tended to bulge through the incision because of the distention. The appendix appeared normal. When the sternum was removed, the left lung collapsed partially, while the right lung was distended, occupying the greater part of the mediastinal space and extending over to almost the left lung. On opening the pericardial sac, a thickened pericardium was observed and an excess of straw-colored fluid.

The lungs were removed without difficulty. No adhesions on either side were evident, except slight recent diaphragmatic adhesions on the left. A small amount of clear straw-colored fluid was present in the right pleural cavity. In removing the lungs, numerous calcified tuberculous bronchial glands were found. The azygos system seemed deeply congested, the vessels standing out quite prominently when the lungs were removed. On sectioning the lungs, the left showed beginning cavity formation in the middle third. There were no ruptured bronchial arteries noticed. The lung was firm and the bronchioles and air sacs were filled with a mixture of what appeared to be blood and purulent exudate. The apex

showed numerous contracted areas. The right lung showed marked distention and appeared about a third again as large as when normal. On section, there was marked edema and emphysema. The apex was scarred. The right lung floated when placed in water; the left did not. The right lung was emphysematous while the left showed consolidation and cavity formation.

The heart and thoracic aorta were removed *en masse*. Dissection showed that there was an aneurysm about 2 inches in diameter which had ruptured into the left bronchus, and multiple smaller aneurysms surrounding this larger one. The heart and aorta were placed in formalin 10%, to be examined later.

The liver, except for a slight enlargement, appeared normal on external inspection. On section it cut with a little greater resistance than normal. The whole organ showed a marked congestion. The spleen was soft, "mushy" and congested. There was just beginning fibrotic change evident. The kidneys were rather large and congested, and on section, disclosed a beginning acute diffuse nephritis with chronic changes. The glomeruli stood out prominently. The stomach contained a considerable quantity of blood and mucus, but otherwise appeared normal. The mesenteric lymph nodes were caseous. The intestines were distended with gas and showed no other pathologic changes. The prostate and the testicles were normal.

The hardened heart and aorta, on dissection, presented the following:

The heart showed slight dilatation and hypertrophy of the left ventricle. The papillary muscles were pale. The tricuspid valve showed thickening and fibrotic changes. The mitral was in good condition,—clear and thin. The coronaries showed no marked pathological changes. Just above the middle aortic valve was a beginning aneurysm of 15 mm. in diameter. In a direct line up the aorta about 25 mm., another small nonperforating aneurysm appeared. The transverse portion of the arch of the aorta appeared as several coalescing aneurysms, one large, almost perforating, one at the apex, 5 cm. in diameter, and the perforating aneurysm on the base, 4 cm. in diameter. The perforating aneurysm extended posteriorly and ruptured into the left bronchus just below the bifurcation of the trachea. The ascending portion of the aorta showed a marked thickening and dilatation. Numerous whitish opaque patches were scattered over the entire surface. The descending aorta showed a marked thickening and dilatation.

*Anatomic Diagnosis.*—Multiple aneurysmal formations of aorta; ruptured aneurysm into left bronchus; syphilitic aortitis; cardiac dilatation and hypertrophy; hemorrhage; pericardial effusion; emphysema; tuberculosis with pneumonic changes of left lung; passive congestion of liver and spleen; acute diffuse nephritis.

#### REMARKS

In this case lues was denied, but gonorrhea had been acquired 10 years before the onset of the dyspnea, the pain over the heart and in the back, and the cough, which seemed to be the essential symptoms.

#### CASE VII

G. C., Hospital No. 178202, a white man, 37 years of age, was admitted to the Cincinnati General Hospital on March 2, 1913. This was his second admis-



sion for the same condition. He complained of swelling of the feet and shortness of breath.

*Family History.*—His father died of stomach trouble, his mother of old age. He had one brother and one sister still living and well.

*Past History.*—At the age of 22 he had "typhoid pneumonia" for 13 weeks; mumps at 14 with a complicating left orchitis; a chancre at 20. For the latter affection he had been treated by a physician. He had used a glass of beer daily and occasionally drank a glass of whiskey.

*Onset.*—In February, 1912, he noticed that he was short of breath. If he worked hard or walked up steps he felt as though his breath would not come fast enough, and he had to rest. Swelling of the feet and ankles came on suddenly during the latter part of March.

*Status Præsens.*—On entrance he appeared as a well developed and well nourished white man, weight 145 lbs.; height 5 ft., 9 in. Respirations 25, pulse 90, temperature 98° F. There were no unusual appearances connected with the head, eyes, ears, nose, or mouth. Examination of the neck was unproductive. The chest was well developed, and equal on both sides. There were no pulmonary symptoms or signs. The apex impulse was diffuse but appeared in the sixth interspace about one and one-half inches below the nipple. The first sound was accompanied by a long blowing murmur, and the second sound was short. All the sounds were very loud and rapid. The heart dullness extended about a finger's breadth to the right of the sternum; as low as the sixth interspace below, and to the third interspace above. The blowing murmur was best heard in the fourth interspace to the left of the sternum. The abdomen was not rigid. The spleen was palpated with a little difficulty and was slightly enlarged. The abdomen was somewhat tympanitic. The legs were edematous.

Clinical notes in the history indicated that between Oct. 29 and Nov. 14, 1912, the patient's condition was fairly good, and that the pulse became slow with rest and quiet. On Nov. 29th the swelling of the legs was more noticeable and an x-ray showed an evidently enlarged heart. Between this date and Jan. 15, 1913, the edema progressed upward until the thighs and scrotum were involved. On Jan. 18th a salt-free diet was started and from that time till Feb. 23rd improvement was rapid and continuous; the edema disappeared and the patient was discharged. He returned and was readmitted on March 2nd with general edema involving even the face. Two days later, at 10 A. M., he suddenly had a convulsion and died 20 minutes later.

*Clinical Diagnosis.*—Aortic and mitral insufficiency.

#### AUTOPSY PROTOCOL (A)

(Permission was given to remove only the heart.)

The heart weighed 1025 grams, and measured 19.25 cm. in greatest length and 14.37 cm. in greatest breadth. About the base of the heart there were numerous petechiæ. The right ventricle was more dilated than the left. The myocardium was generally hypertrophied. There were no obvious valvular abnormalities. The aorta was the seat of a well marked luetic aortitis. The coronaries were apparently healthy.

At the base of the lateral aortic leaflet was a fenestrated oval opening measuring 1.87 by 1.57 cm. in diameter. This opening led into a sac situated between the ventricles immediately below the auriculoventricular groove. Immediately above the same aortic leaflet was an oval opening, 1 by 1.6 cm. in diameter, which also led into the sac. This opening was evidently the older and the edges were smooth and firm. The sac measured 4 cm. in diameter, and its walls were free from thrombi and studded with hyaline plaques, and patches of calcification.

*Anatomic Diagnosis.*—Hypertrophy and dilatation of the heart; luetic aortitis; aortic aneurysm perforating into the left ventricle.

#### REMARKS

In this case the first symptom, shortness of breath, appeared sixteen years after the primary infection.

#### CASE VIII \*

W. J., Hospital No. 152041, a colored man 40 years old, was admitted to the Cincinnati General Hospital, on Oct. 27, 1909, complaining of pain in the left side and shortness of breath. He died three months after admission.

He gave a history of the usual diseases of childhood, of smallpox, rheumatic fever, gonorrhea, and syphilis. Shortness of breath commenced 5 weeks before admission, and thereafter became more pronounced and was associated with cough and night sweats.

On admission, the temperature was 96.8° F., pulse 96 and respirations 32. The thorax was symmetrical. Respiration was labored, but the respiratory movements of the thorax were of normal extent, except in the right axillary region when they were diminished. The percussion note was flat in the left axilla. There was a friction rub on the left side, and, in this region, low in the axilla, the breath sounds were distant. The outline of cardiac dullness was increased both vertically and transversely. The apex beat was felt in the sixth intercostal space, close to the axillary line; it was forcible, strong, and regular, and fairly well circumscribed. At the apex an inconstant soft systolic bruit of varying intensity could be heard. At the level of the junction of the fourth rib and at the sternocostal junction, a rough systolic and prolonged and somewhat smooth diastolic bruit were heard. Both of these varied considerably in physical properties, at times being almost inaudible, and, again, loud. The aortic diastolic bruit occasionally disappeared. Percussion showed an abnormal area of dullness above the base of the heart. The pulse was regular, full, large, and strong—a typical Corrigan.

At the time of admission, there was no edema of the legs. Later, the patient became more and more short of breath to the extent that sleeping was interfered with. Still later dyspnea made it necessary for him to assume a sitting position at night, and vomiting commenced and continued intermittently. The respiratory symptoms gradually increased in severity; the systolic murmurs at the

\*This case was reported by Woolley and Newburgh in *The Dandridge Memorial Volume of the Cincinnati Research Soc.*, 1912, p. 119.

apex became quite regular, soft, and smooth. To the right of the nipple, a rough systolic and a diastolic murmur could be heard. The aortic diastolic murmurs became less intense, and a pericardial friction developed. The legs became more and more edematous; the edema constantly extended toward the body, and gradually the patient became weaker, sank, and died.

At no time was there sugar or albumin in the urine though the specific gravity reached 1030.

The *Clinical Diagnosis* was syphilitic aortitis, aortic stenosis and regurgitation; passive congestion of the kidneys.

#### AUTOPSY PROTOCOL

The autopsy was done two hours after death. The report was, briefly, as follows:

The body was that of a poorly nourished middle-aged negro. The lower part of the body from the umbilicus down, was enormously swollen, edematous, and covered with large blebs. Postmortem rigidity was commencing in the hands, but elsewhere was absent. The peripheral lymph glands were not enlarged. The prepuce was edematous and phimotic. The glans penis showed numerous small shallow ulcerations and scars. The abdomen contained about 100 c.c. of a reddish brown clear fluid. The pleural cavities were filled with a similar fluid. In the pericardial cavity there was a considerable amount of a clear straw-colored fluid. There were no pleural adhesions. The lungs were moderately edematous but showed no other changes. The liver was of normal size, was quite firm, and of a pale brown color marked with small hyaline areas which stained brown with iodine. The spleen was a typical sago spleen. The kidneys weighed 185 grams each. They were quite firm, of a purplish red color and the cortices were widened. The glomeruli appeared as enlarged hyaline shining points which gave the amyloid reaction. The heart was enlarged, pale, and flabby. It was bilaterally dilated, and, in addition, the left ventricle was hypertrophied. The myocardium was greatly fibrotic. The cardiac orifices showed no unusual changes. All were apparently somewhat dilated, especially the tricuspid.

The aorta was the seat of an extensive and severe grade of arteriosclerosis of the luetic type. Just above the mouth of the left coronary was the opening, 5 cm. in diameter, of an aneurysmal sac which was 7 cm. in diameter. In it were no clots. The walls were irregularly sclerosed and marked by scattered hyaline plaques and atheromatous ulcers. The aneurysm projected laterally to the left, and was adherent to the pulmonary artery through the wall of which were two openings at a point about 1 cm. above the junction of the posterior and left leaflets. These openings measured 1 by 2 cm. and 1 by 2 mm. in diameter. The margins of both were smooth and showed no evidence of recent rupture. The pulmonary artery showed both fatty degeneration and hyaline sclerosis, especially just about the aneurysmal openings.

*Anatomic Diagnosis.*—Aortic aneurysm with perforation into the pulmonary artery; syphilitic aortitis; amyloidosis; passive congestion of the liver, kidneys, and spleen; hypertrophy and dilatation of the heart; pleural and pericardial effusions; edema of the lungs.

## REMARKS

In this case there was an admitted history of lues, but there was no note in the history as to when it was acquired. The first symptoms were shortness of breath, cough, and pain in the side.

## CASE IX.

L. C., Hospital No. A-8264, a white widow, aged 32, a shoe-worker, was admitted to the Cincinnati General Hospital, December 14, 1916, complaining of "cough" and "pleurisy."

*Family History.*—Unimportant. The patient's husband was dead. She had no children and had never been pregnant. She had never had a serious illness until the present one.

*Present Illness.*—About three weeks ago the patient had a severe chill which lasted about a half hour. With this she had a high fever. For a number of years she had had a slight cough. This grew worse after the chill, but there was no expectoration. Soon after the chill she suffered with severe pain in the left side, starting in the back and radiating through the axilla to the front of the chest. The pain was worse when the patient was lying on the left side. The pain would disappear for a day or more, and then return. A hard coughing spell would sometimes bring it on. The patient took patent medicine for some time but without relief. About two days before the admission the pain in the side became less severe. The cough was also better but was troublesome during the night. Throughout her illness she had frequent severe headaches and fever. Her bowels have always been constipated.

*Physical Examination.*—The patient was a well developed, well nourished woman lying quietly in bed. Respirations were frequent and shallow, not labored. There was a herpes vesicle beginning on the upper lip. There was a slight movement of the alæ nasi. The pupils reacted to light and accommodation. The scleræ were clear. The mucous membranes and skin were of fair color. The ears were negative. The teeth were in fair condition. There was some pyorrhea. The tongue was moist and coated. There was no general glandular enlargement. The thyroid was not enlarged.

The chest was well formed and symmetrical. Expansion was somewhat diminished in the left axilla. Over the left upper front the note was slightly higher pitched than on the right. There was good resonance in the left axilla to the 8th interspace. The right front and sides were resonant on palpation. Traube's space was clear. On auscultation there were expiratory moist râles in the left lower axilla with decreased vesicular breathing over the upper left; there was strong vesicular breathing throughout the right front. With the patient sitting, the left base posteriorly was dull, the dullness beginning at the middle of the interscapular space. The dullness was very pronounced although not absolutely flat. Percussion over the spine gave dullness beginning at the 6th dorsal. There was a well marked Grocco on the right. Vocal fremitus was diminished over the upper part of the dull area and slightly diminished over the lower. There was no

egophony. There was good vesicular breathing throughout the right back. Above the dull area on the left there was bronchovesicular breathing. Over the dull area there was very distant bronchial breathing which was just audible. In the upper left axilla a few fine moist râles were heard on coughing.

The heart apex was neither seen nor felt. Relative cardiac dullness extended 4.5 cm. to the right in the 4th space, and 11.5 cm. to the left in the 5th. There was a short soft systolic blow following the first sound at the apex. This was transmitted a few centimeters toward the axilla, but not toward the base. The second sounds were equal and of moderate intensity. The radial pulses were regular in force and rhythm, of moderate tension, and rather frequent. Blood pressure, systolic 110, diastolic 70.

The abdomen was on the level with the ribs. The liver and spleen were not felt. There was no rigidity or tenderness.

A needle was inserted in the left base in the 9th interspace at about the scapular line. A small amount of thick yellow material which was blood-tinged was removed. Examination showed many pus cells.

Urine: neutral, yellow, clear, specific gravity 1020, no albumin, no sugar.

Blood examination shows red cells, 5,216,000, hemoglobin 90%, leucocytes 14,000. Differential count shows lymphocytes 4%, large mononuclears 3%, transitionals 3%, polynuclear neutrophils 88%, eosinophiles 2%.

The patient's temperature was 103.2°, pulse 132, respirations 36.

A diagnosis of empyema was made and operation was advised. On December 16, the patient was transferred to the surgical service. Under ether a 2½ inch incision was made in the left back. Part of the rib was excised. The pleura was carefully opened. No free fluid or pus escaped. On insertion of the fingers, adhesions of the pleura were found. The lung felt infiltrated. At this time there was a sudden gush of blood from the mouth and nose followed by extreme cyanosis and death in a few moments. There was practically no hemorrhage from the operative wound.

*Clinical Diagnosis.*—Empyema (left pleura).

#### AUTOPSY PROTOCOL (McC.)

The body was that of a well developed, well nourished white female, about 34 years old. Postmortem rigidity was slight; lividity was slight in the dependent portions. There were no scars. Over the left median basilic vein there was an incision about 2 cm. long. There was a second incision closed with four sutures, which began at the midaxillary line in the 7th interspace and extended backward about 6 to 7 cm. This incision, when opened, disclosed a resection of the 7th rib. The mucous membranes of the body were pale as was the skin over the entire body. The teeth were in good condition.

On opening the thoracic cavity, the left lung was not collapsed; the right showed considerable emphysema. The heart was in position; the liver extended below the tip of the sternum perhaps 6 cm. and in the midaxillary line, was 4 cm. below the costal margin. There was no excess of fluid either in the thoracic or abdominal cavity. The appendix was in position and apparently normal. The

bladder was not distended. There were several small fibroid formations on the uterus.

On removing the right lung, it was found free, very light, and emphysema was quite marked. Cut section disclosed nothing more than an exceedingly marked emphysema, the lung tissue itself being healthy. The left lung presented adhesions low down posteriorly and diaphragmatically, of recent origin. The lung, when removed, was quite heavy, solid, and crepitated only slightly at the apex. It was of a mottled dark red color, and the base, particularly, felt very solid. There was no pus or excess of fluid present in the pleural cavity, and the 7th rib showed a clean resection at about its middle portion, perhaps 4 cm. having been removed. Cut section through the left lung proved it to be involved in multiple abscess formations. It was quite firm and mottled pink-gray in color. The surface was bathed in pus which flowed from the smaller bronchi and from the lung tissue itself. This condition was present in the upper lobe to a considerably less extent.

The heart presented no marked abnormal changes. The muscle was pale but of good quality, and the valves were apparently in good condition. The aorta throughout the ascending portion presented a few plaque formations, and at the distal end of the transverse portion on the lower aspect there was a small ruptured aneurysm about the size of a dollar. The sac of this projected downward about 2 cm. and had ruptured through a rounded mass of clot into the left bronchus. The organized clot seemed to be well rounded, did not present any fragmentation, and almost occluded the left bronchus at a point about 4 to 5 cm. from the bifurcation. The abdominal aorta presented a very thin wall, but otherwise seemed normal.

The liver was slightly enlarged and on cut section quite pale. The spleen was pink, pulpy, and slightly enlarged. The kidneys were larger than usual, pale, the capsules stripped easily, the cortices were somewhat diminished, and the medullæ pale. On section, the organs were rather pale throughout. The intestines were not opened. There were no stones in the gall bladder.

*Anatomic Diagnosis.*—Aneurysm of the aortic arch ruptured into the left main bronchus; luetic aortitis; pulmonary abscesses (aspiration pneumonia); acute fibrinous pleuritis; chronic diffuse nephritis; costotectomy.

#### REMARKS

In this case there was no history of lues. The patient had had a slight cough for some years and then suddenly she had a chill which was followed by pain in the left side and back.

#### SUMMARY OF CASES

In this series of cases presenting perforating aneurysms, nine in number, the ages were as follows: twenty-seven (No. 2366); thirty-two, (No. A-8264); thirty-five, (No. 6524); thirty-seven, (Nos. 178202 and 5872); forty, (No. 152041); forty-two, (No. 4719); and forty-three, (Nos. 5444 and A-5262). Three of the patients were white

(Nos. 5444, A-8264, and 178202). Two were women (No. 2366, A-8264), one of them (No. 2366) the youngest in the group. In three cases, Wassermann reactions were done (Nos. 6524, 2366 and 4719) and in each it was positive. In all, however, the anatomic evidence of lues was decisive, for in each case the aorta showed macroscopically typical aortitic plaques, and sections showed the presence of typical vascular and medial lesions. Also, three cases other than those in which Wassermann reactions were done admitted syphilitic infection (Nos. 5262, 178202, and 152041).

SOME REMARKS ON THE SEROLOGICAL DIAGNOSIS OF  
SYPHILIS WITH SPECIAL REFERENCE TO  
THE HECHT-GRADWOHL TEST\*

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IN a serious consideration of the influence that serology has brought to bear upon the practice of syphilology during its comparatively recent connection with medicine, about eleven short years in all, it is necessary in retrospect to consider exactly how much was known of this interesting disease before the days of its serum diagnosis, compared to what is known about it today. Rather would I ask, how much knowledge was there of syphilis before the epoch-making discovery of the spirochete pallida by Schaudinn and Hoffmann<sup>1</sup> in 1905? The date of the discovery of the causative organism of this disease in 1905 and that of the publication of the work of Wassermann, Neisser and Bruck in 1906, so closely approximate, that for practical purposes we may consider them simultaneous discoveries in reviewing the "prelaboratory" days of syphilology. Those who were actively concerned with the handling of syphilis before 1906 perhaps have forgotten their earlier teachings. An upheaval in matters medical or political that is followed by a permanent change for the better often causes such a readjustment of one's mental views that the passage of a decade often suffices to cast a shadow over the past, dim yet so impenetrable that one finds difficulty in ever piercing it by memory's processes. For this reason let us take down our textbooks that were in use up to 1905 and let us scan hastily the then-existing authoritative words of our masters in medicine. It is undeniable that the clinical symptomatology of primary and secondary syphilis was well described even by the ancients in medicine. The primary sore, the so-called Hunterian chancre, was so well pictured that it could be glibly described by even the novice in our ranks, in the old days. The various manifestations of

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syphilis of the skin and the mucocutaneous orifices were graphically described in our books, and illustrated in our clinical minds' eyes. The characteristic gummatous lesions of the skin *intra vitam*, and the undeniable gummata of the viscera at the autopsy table were familiar to all of us who attended these syphilitics in the out-clinics and the hospital wards of our eleemosynary institutions and who followed so many of them to autopsy in the dismal morgues of these institutions where were studied the gross anatomic changes of visceral syphilis. The manifestations of syphilis of the nervous system were *suspected* in many cases. Many writers believed in the luetic origin of tabes dorsalis, and still others stoutly maintained that general paralysis of the insane was evidently of syphilitic origin. The subject of visceral syphilis engaged the attention of some of the more acutely observing internists of fifteen or twenty years ago. It will be recalled, however, that these observations were largely based upon anatomic study at autopsy and not upon symptoms in the living subject. The first description of the anatomical changes in the syphilitic is given by Gubler of Paris in 1847, a description of the lesions of congenital syphilis of the liver. Dittrich, of Prague, in 1851, followed with a description of acquired syphilis of the liver. The first really classic description of syphilis in the various large viscera was given by Virchow<sup>2</sup> in his fifteenth volume of his Archives, as long ago as 1858. Comparatively little was added to this description of Virchow up to the time of recent investigations, namely, within the past ten years.

It is curious to note that in these up-to-date volumes published prior to 1904, a great deal more attention was paid to hereditary than to acquired syphilis. The thought of the medical world seems to have been morbidly concentrated upon the lesions and diagnosis and treatment of congenital lues, almost to the exclusion of that of acquired lues. The congenitally infected individual seems to have caught the diagnostic and therapeutic eye of most of the older syphilographers. I may perhaps be fully able to explain this later on in my remarks.

There seems also to have been a perfect understanding of the manner of transmission of this disease, its contagiousness in the primary state; the extreme danger to his fellow-man of the individual with lesions of the mucocutaneous orifices was apparently fully appreciated. The frequent incidence of examples of infection by this means and possibly the frequent practice of confrontation of the older days un-

questionably were factors in definitely proving this point. The question of the transmission of syphilis from parents to offspring aroused great interest and was the subject of much discussion in the older books. Our conception of the curious phenomena of parental and congenital lues was completely swayed by the two celebrated laws, that of Collès-Baume,<sup>3</sup> expounded in 1837, and that of Profeta<sup>4</sup> issued in 1865. According to the former, "syphilitic children did not infect their mothers." This was true, not because Collès' fundamental explanation was true, that an immunity existed, but *because the mothers were always already infected*. Under Profeta's law, a healthy child of a syphilitic mother was immune to syphilis, but ceased to be immune at puberty. We understand, of course, now that this law is clearly and absolutely in error.

In general it may be said that prior to 1905-6, there was an exactitude in description of the *typical* lesions of this protean disease coupled with a rather vague understanding of many considerations of the subject due to a complete absence of knowledge respecting the microbiology of the disease. Clinicians and pathologists had apparently exhausted their powers of description of visible lesions during life, and gross lesions at autopsy. Coupled with the fact that syphilis was sometimes *suspected* as being the causative factor of certain symptom-complexes, there were always the associated factors at hand of Bacchus, Venus, Vulcan and other mythological personages usually taken as representative of human bad practices, upon which the onus of these disease manifestations could be placed in almost any instance; if the individual was too young to have acquired these vices, then the vices of his progenitors were straightway made responsible for his physical disability. The idea was not at all clear in those days that these vices, while possibly causative in the sense that the primrose path of dalliance which these individuals were treading brought them in contact with the spirocheta pallida, did not in any sense *cause* the manifestations which today we know are completely and solely due to the ravages of the syphilitic microorganism.

So far as the treatment and the estimation of the cure of a case correctly diagnosed as syphilis was concerned in those days, which I trust I may be pardoned for calling the "prehistoric" days of syphilology, the older textbooks will again serve to refresh our memories, if the multitude of living disabled survivors of our earlier fruitless

therapeusis are not in themselves sufficiently convincing proofs. We read that mercury and iodide of potassium were specifics—and in a sense they were, and still are to this day. And then we read in those tomes of older days of the great difficulty of handling some of these cases with these drugs; of the fruitless efforts at times to eliminate visible lesions of syphilis even though the various methods of introducing mercurials into the body were used; we read, too, of the age-old question that the conscientious practitioner put to himself with respect to these sufferers; how may we know that these individuals are well? The question of attenuation of the disease in the untreated and in the treated was argued through page after page of our books. Many authorities, Taylor among others, gave testimony of observations of perfectly healthy persons bearing unmistakable marks of former manifestations of syphilis, who were totally unconscious that they ever had such a disease as syphilis, and had never undergone any treatment to eradicate it. The doleful cry of the writer of the pre-Wassermann days continually rang out, that the noninoculability of syphilis on other than human beings made it doubtful whether we shall ever be able to divest syphilis of its sharpest sting, of its direst curse, its uncertainty. These men appreciated fully that they stood helpless in their understanding of this disease without the knowledge of its causative factor and the biological phenomena that this causative factor probably induced in the circulating fluids of infected individuals.

In 1905 Schaudinn and Eric Hoffmann<sup>5</sup> discovered the presence of the spirocheta pallida in syphilitic lesions. This has since been confirmed so that it is now accepted as the microbic cause of syphilis. Following closely upon this discovery came the remarkable publication by Wassermann, Neisser and Bruck<sup>6</sup> in 1906, wherein it was shown that the very interesting experiment of Bordet and Gengou,<sup>7</sup> on complement fixation could well be applied to the diagnosis of syphilis. Wassermann and his coworkers maintained that in the blood sera of syphilitic individuals there was a substance which he called an antibody which if brought into contact with an extract of a syphilitic organ, called an antigen, "bound" complement so that the later addition of an animal's corpuscles and its homologous amboceptor serum was not followed by hemolysis such as would have occurred had the complement been "free" or "uncombined" or "not anchored," as the terms are variously used. With the publication of his paper and a de-

scription of the technic employed in making this test, that new department of laboratory methods known as serology really saw its birth. There sprang up rapidly a tremendous array of workers who tried out the Wassermann test in syphilitic and nonsyphilitic individuals. For a long time, the test hovered upon the edge of the bottomless chasm into which so many medical discoveries have been precipitated, never again to be heard of. Reports came thick and fast into the literature from masters and fledglings in this new-born science, reports of the startling findings of this reaction in many diseases other than syphilis. The test fell into the hands of the unscrupulous who used it for personal gain, ever mindful of the century-old lay dread and terror of this disease. Miraculous to state, another epoch-making discovery came to us while this strife was being waged, the Ehrlich-Hata preparation known as salvarsan, or 606, or arsenobenzol. The battle to establish or to destroy the Wassermann test seems in some manner to have been markedly influenced for the better by the *failure* of Ehrlich's preparation to be the *therapia magna sterilisans* that he hoped it would be. The very fact that there were positive Wassermann reactions preceding recurrences of syphilitic lesions after salvarsan medication, pointing the way, as it were, to the doctrine of the noncurability of all cases of syphilis by one or one hundred doses of salvarsan, seemed to jolt the jaded minds of the profession into a belief that after all, there *was* something specific in the Wassermann technic.

Out of the sea of uncertainty that existed after 1906, there gradually came to light certain truisms concerning this reaction. The grossest manipulative errors had been made by unskilled workers, and yet as Vedder<sup>8</sup> has said, "One is impressed by the fact that the Wassermann reaction must be a test of most surprising merit to have survived all the clumsy technic that has been perpetrated in its name." It is today recognized as a test that if found positive indicates syphilis; if negative, unfortunately, it does not necessarily exclude syphilis. If properly performed, it is found present in almost all cases of syphilis associated with cutaneous manifestations, corresponding to what has been called the secondary stage of syphilis. It is rarely found in the stage of secondary incubation before the fourteenth day; it is found in a great many cases of tertiarism. With respect to its absence in the stage of secondary incubation, this is of but little moment provided we have opportunity to search for



Fig. 1.—Dark-field apparatus with Gradwohl arc lamp for demonstration of *Spirochete pallida*.



the spirochete pallida in the secretion of the primary lesions; by dark-field illumination, this organism is readily identified. The reaction of Wassermann is found in a small percentage in the blood serum of tabetics and in practically all sera of paralytic dementes. If it is not present in the blood, it surely will be found in the spinal fluid of over ninety-eight per cent of these patients.

Let us now look upon this picture and upon that, upon the picture that we presented of syphilology prior to the discovery of the manner of making this test, and the picture since the practical details of making the test properly have been worked out. In the older days, we looked at a lesion and wondered if it was syphilitic; at the present time we take some of the serum from such a lesion and look for the spirochete with the dark-field apparatus and *find* it if the lesion is syphilitic. No longer do we look for "classical Hunterian earmarks." No longer do we roll the lesion between the finger and agitate ourselves over the diagnostic value of its induration--incidentally no longer do we so infect ourselves by this useless and dangerous practice. No longer do we depend upon a nonpathognomonic adenopathy, inguinal, postcervical, or epitrochlear, for our early or late diagnosis. If the case has progressed to general adenopathy, it is reasonable to expect a reaction in the blood. If we find it, or if we have already found the spirochete pallida in the lesion, we immediately resort to antisymphilitic treatment. No longer is it necessary to await the onset of secondary manifestations. Rather do we seek to prevent them by adequate treatment once the diagnosis is made by microscopic or serologic methods. The hope of a *therapia sterilisans magna* can most certainly be attained in many cases if early scientific diagnosis of syphilis is made and if adequate intensive treatment is applied. Again, by means of this test, we can control our treatment of the syphilitic by frequent blood tests, not waiting for the appearance of a positive, once a negative is obtained; but by piling Ossa upon Pelion with more and still more treatment in the hope of obtaining one negative Wassermann after another, we endeavor to stamp it out. In no other way can we accurately survey the course of antiluetic treatment. So much for the difference in our present methods with respect to the diagnosis and treatment of primary and secondary syphilis, as compared to the methods of the past.

As regards the diagnostic value of the Wassermann test in the consideration of syphilis of the internal or covered parts of the body, it has been of most supreme value. In the former days, we were told to examine the patient carefully for syphilis, glands, tongue, mouth, search for sears, attention being given to the long bones, lungs, the cardiovascular system, the size of the liver and spleen, of course, not overlooking the other palpable viscera. After this, what could be done? The application of the therapeutic test could be carried out, but this was unsatisfactory and unsuccessful in many instances. Today, the physical examination is made just as carefully, the blood is taken for a Wassermann test and the result recorded if syphilis is suspected. Obscure visceral manifestations, that were formerly seldom recognized, are today readily explained by means of this test, with the institution of proper treatment and a successful therapeutic outcome. The epoch-making work of Warthin<sup>9</sup> has given us, too, a clearer insight into the necessity of searching for syphilis of the cardiovascular system by means of the Wassermann test, more so than was ever deemed necessary in the "prespirochete" and "pre-Wassermann" days.

As part and parcel of active syphilis of important organs, we must remember the role that has been played by the Wassermann in fastening the proper label upon many obscure symptoms of derangement of the nervous system. Today, the discovery of an irregular pupil, an absent knee jerk, a suspicious lancinating pain, or difficulty in urination with a cystoscopic finding of trabeculation of the bladder, means a quick search for syphilis of the nervous system, a Wassermann test of blood and a Wassermann, globulin, lymphocyte count, and Lange colloidal gold test of spinal fluid. In the presence of any suspicion of involvement of the nervous system, recourse must be had at once to the lumbar puncture needle and the serological test of spinal fluid. Too much emphasis cannot be laid upon this point. To those who dread the frequent use of the lumbar puncture needle, we need but remind them of the responsibility which they are assuming in *preventing* a patient from knowing the exact status of his nervous system by this willful and obsolete hesitancy in taking advantage of a safe and imperatively necessary diagnostic procedure.

Every tabetic and parietic at some time or another in his past has



been a "latent" syphilitic and if so, might have been diagnosticated and treated at that time as such. Every latent syphilitic is potentially a candidate for syphilis of the nervous system or some other viscus. Every one of these latent syphilitics needs treatment—and certainly intelligent treatment cannot be given until a serological diagnosis is made. We hold no brief for any special method of treatment; our theme is to directly point out the advances that have been made in medical diagnosis by means of the Wassermann test. The most monumental sin of which the profession is guilty with regard to failure to properly recognize syphilis is the inclination in some quarters to accept the patient's history or social or marital status as prohibiting the existence of syphilis. Statements of the patients regarding their past histories concerning syphilitic infections may be highly interesting, but they should have but little weight if negative, if we wish to properly search for and find this disease. Firstly, these patients frequently lie; secondly, they may possibly have had a primary lesion which someone incorrectly called a nonspecific sore; thirdly, they may have forgotten that they ever had a sore, and lastly, they may never have seen one. Urethral chancres have unquestionably been overlooked; they are still being overlooked; each one of these patients becomes a latent syphilitic. Again, the old conception that syphilis is always associated with skin manifestations is clearly erroneous. Many of these patients go through the transition of primary sore to "latent infection" without ever having had a skin manifestation. In these cases, of course, the Wassermann test properly performed is better evidence than the incompetent or willfully fraudulent statement of the patient.

There is a fly in all ointments and so we must discuss now the shortcomings of the Wassermann. We have pointed out its splendid helpfulness when positive. Let us discuss the fact that it is sometimes negative in manifest syphilis, that a diagnosis must not be necessarily abandoned when it is found negative, that there are definitely plausible causes for its negative presence in manifest syphilis, and that there are possibly methods of overcoming this apparent shortcoming. To go back to the manner of performance of the test, it must be recalled that the blood of the patient is taken from a vein, centrifugated, the serum removed, the serum heated to 56° C. for the purpose of destroying the natural complement present; that it is now

added to the test tube in combination with the proper dosage of antigen or extract of syphilitic or normal organ, plus artificial complement furnished by the proper amount of guinea pig serum, incubated in dry heat or water bath for half to one hour, hemolytic amboceptor and appropriate corpuscles added, reincubated, and the result read off. It is necessary to add the proper amount of reagents of the kind enumerated in making this test. The estimation of the proper amount of reagents needed is determined by preliminary titration. The use of the proper antigen has been one of the many disputed points among serologists in regard to standardizing this test. The use of an extract of syphilitic organs as an antigenic extract was first proposed by Wassermann, who believed that his test was purely an antigen-antibody reaction. Without altering the specific value of this test in any way, we know now that the Wassermann test is *not* a specific antigen-antibody reaction; on the contrary, the reaction may just as well be brought about by the interaction of syphilitic antibody with antigens made of normal organs prepared in various ways. This fact, while apparently contradicting Wassermann's explanation of the rationale of his test, in no way has reduced its scientific and practical value. Nevertheless, it has given many investigators an opportunity to foist upon their pupils their pet method of making antigens or their particular technique of using them. There are many different schemes of application of antigens to the test. As yet there is no standardized method, so that the result of an examination of blood by different laboratory workers has led to some startling differences in results. This, of course, has not helped in any way to inspire the respect for this test that it really deserves. The very failure to find this test continually present in all untreated syphilis has induced one worker after another to use different antigens, to use more than one antigen in each blood tested; to add cholesterol to the antigens for the purpose of increasing the delicacy of the complement fixation. It has also led some workers to vary the amounts of amboceptor and complement and sheep cells; to vary the amount of patient's serum; to vary the method of incubation, from dry air to water heated to 37-38° C.; it has led some to utilize the method of carrying out the test in the ice box; many devices, in short, have been resorted to in an endeavor to enhance the accuracy of the test and to obtain the highest possible percentage of *correct* positive reactions.

Like others in this line, I have endeavored to ascertain what method promises the best results, although I must confess that the use of the classical test as laid down by Wassermann with but few modifications, seemed to me for many years to give the best results. I was, of course, ultimately brought face to face with the fact that in a number of cases I obtained negative reactions with blood sera that came from actively syphilitically infected persons. In something like ten years' wide experience with the serologic specialty, I have found the Wassermann positive in but sixty per cent of all syphilitic persons. I have been for a long time convinced that this failure to label lues by means of the Wassermann test was due to some flaw or flaws inherent in the test itself. During my last Continental visit, my attention was called to the method of Hecht and Weinberg<sup>10</sup> in the serologic diagnosis of syphilis. Upon returning to America, I became convinced that there was sufficient evidence in their test, crude though it appeared to be, to warrant a very thorough revision and investigation. To this end, after considerable experimentation, I worked out a modification of their technic and gave it a thorough trial with most gratifying results. I must here explain the scientific principle which they took advantage of in their test and which I utilized in my modification, based upon the following facts: In the endeavor to use exact quantities of reagents in the Wassermann, we inactivate or heat the sera to 56° C. for half an hour to destroy the complement. It is true that this destroys the complement, but it does not take into account the fact that some of the syphilitic antibody is thermolabile or destroyable by heating; and that in the presence of a syphilitic serum containing mainly thermolabile antibody, the entire substance which is to give us a positive reaction is destroyed; ergo, we have a negative reaction in a manifest syphilitic case. Vladimir Busila,<sup>11</sup> as long ago as 1910, called attention to this fact, that in both blood and spinal fluid there are two syphilitic antibodies, one thermostable or unaffected by heat, the other thermolabile, or destroyed by heating to 56° C. He stated that one or both may be present and in various proportions. The thermolabile is the first to appear in the blood and the last to disappear under treatment. He stated that when the thermolabile amboceptor is present alone or nearly alone, the Wassermann reaction with heated serum gives a negative result, but without heating, a strongly positive result. He

also stated that the thermolabile antibody often exists alone in cases of latent, inadequately treated, or nervous syphilis, and the Wassermann reaction performed with the original technic is thus unavailable, precisely in the cases in which it is most needed. Noguchi,<sup>12</sup> discussing this question, showed after considerable experimental work that the syphilitic antibody is greatly reduced by heating to 45° C. At 50° C. it is reduced to one-half, at 55° C. to one-fourth. He also showed that the rate of destruction of antibody at a temperature of 55° C. at five, ten, twenty, thirty, and sixty-minute periods, was as follows: it is greatest during the first five minutes, during which time the antibody strength is reduced about one-third of the original; after thirty minutes it has been reduced about one-fourth to one-fifth, and at the end of one hour to about one-tenth of the original.

Another flaw inherent in the Wassermann test itself is the fact that there is no estimation of the amount of natural amboceptor present in the patient's blood serum under investigation. While competent workers always carry out very exact titrations of the artificial amboceptor which is used in the test, they usually completely disregard the unknown factor of natural amboceptor. The method of Hecht and Weinberg and myself which for the sake of brevity of expression has been called the Hecht-Gradwohl test takes this factor into most important consideration. In this modification I have taken into account the exact quantity of natural amboceptor present, the exact quantity of natural complement present, and, remembering the principles laid down by Hecht, Weinberg, Busila and Noguchi, and others, I have used unheated serum so that no part of the syphilitic antibody may be destroyed. In my first publication<sup>13</sup> on this question in 1912, I reported on the basis of one thousand comparative results with the Hecht-Gradwohl and the Wassermann methods. In my second publication<sup>14</sup> before the American Medical Association in 1916, I based my observations upon about six thousand comparative tests. The present remarks are based upon ten thousand comparative tests with both methods, using the strict Wassermann technic with a dosage of 0.2 c.c. patient's serum, 0.5 c.c. being the amboceptor unit, with a fixed amount of amboceptor and a variable amount of complement dependent upon its daily titer, using always guinea pig serum, which in the presence of 0.5 c.c. of amboceptor would hemolyse



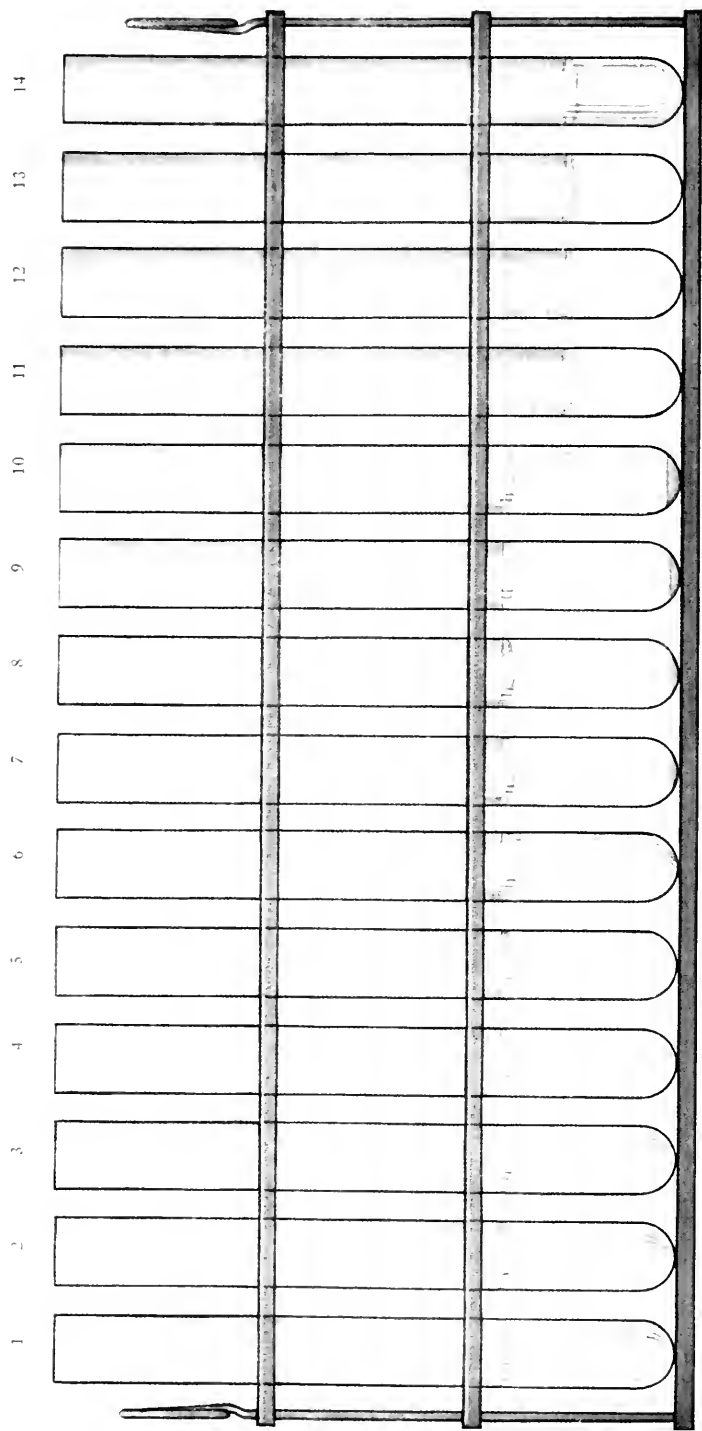


Fig. 2. This illustrates a negative Hecht-Gradwohl reaction with a hemolytic index of "6." It will be noted that "6" is called the hemolytic index because complete hemolysis has occurred in the first six tubes. Note that in tubes 7, 8, 9, and 10 there is respectively an increasing deposit of corpuscles due to lack of hemolysis in these tubes. Also note that tubes 11, 12, and 13, which are the tubes in which the reaction is carried out, show complete hemolysis. Tube 14 shows complete hemolysis because this is the "serum control." (Illustration by Paul P. Halleck.)

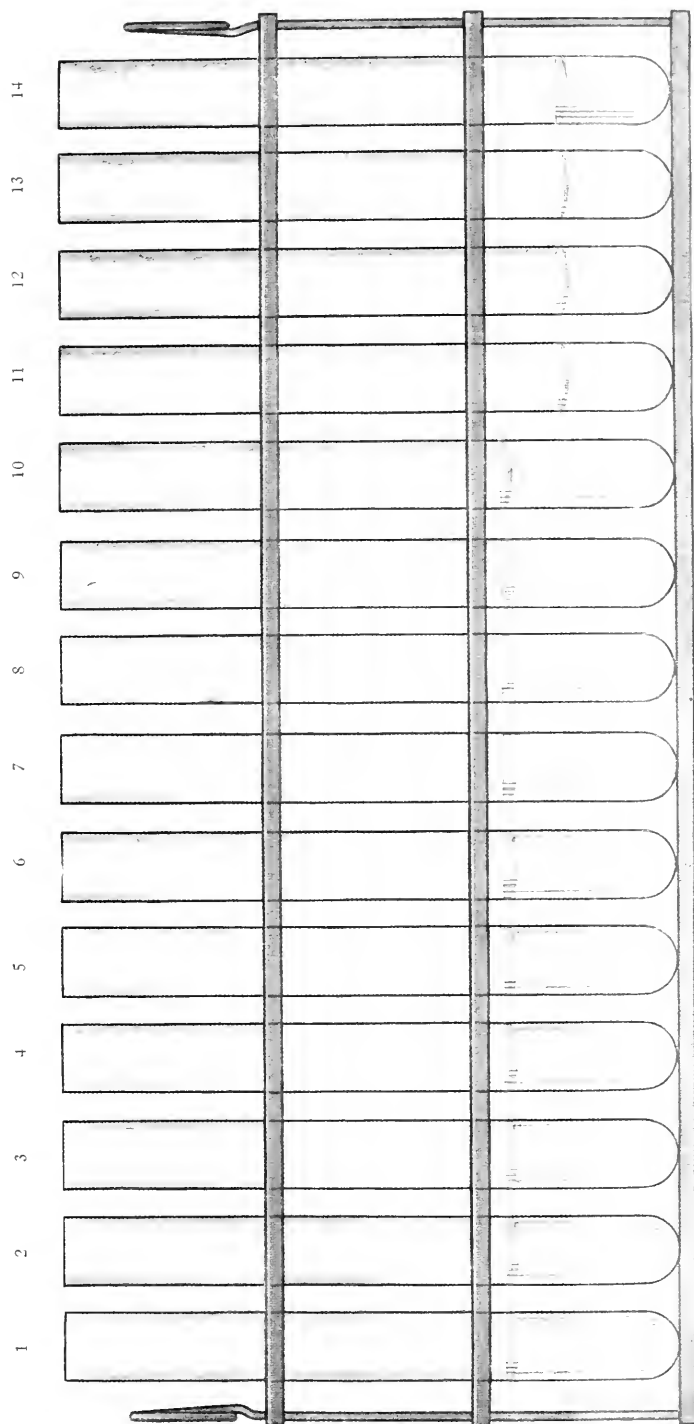


Fig. 3. This illustrates a Hecht Gradwohl positive reaction with a hemolytic index of "6." It will be noted that "6" is called the hemolytic index because complete hemolysis has occurred in the first six tubes. Note that in tubes 7, 8, 9, and 10 there is respectively an increasing deposit of corpuscles due to lack of hemolysis in these tubes. Also note that tubes 11, 12, and 13, which are the tubes in which the reaction is carried out, show a complete inhibition of hemolysis, or a positive reaction. Tube 14 shows complete hemolysis, of course, as it is the "serum control" tube. It may be mentioned that where syphilitic antibody is extremely scanty in amount, due either to prolonged treatment or to attenuation of the disease, one may note in a positive reaction a very slight inhibition in tube 11, a little more in tube 12, and complete inhibition in tube 13. In other words, we have here an extremely delicate and reliable titration syphilitic antibody. (Illustration by Paul F. Hallock.)





1.0 c.c. five per cent sheep corpuscle suspension, in a dilution of 1 to 10 which would be effective always in less than 0.5 c.c. amounts. The Hecht-Gradwohl technic which I have already described in my previous publications is as follows:

Place in a rack fourteen small test tubes. The first ten of these tubes are used to determine the hemolytic index of the suspected blood. By this I mean the exact amount of hemolytic amboceptor present in the given blood serum. The last four tubes are used in the actual test. Add 0.1 c.c. of fresh unheated patient's blood serum to each of the first ten tubes. Then add decreasing amounts of normal salt solution to these tubes, beginning with 1 c.c., then 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2 and 0.1 c.c. to the succeeding nine tubes. Next add increasing amounts of fresh 5 per cent suspension of sheep's blood, starting with 0.1 c.c. and ending with 1 c.c. Place the rack in the water bath for one-half hour. The tube which last shows complete hemolysis constitutes the "hemolytic index;" if it is tube 4, the index is 4, because this tube had received 0.4 c.c. of sheep corpuscles and therefore we have obtained an idea as to how much sheep blood is to be added to the last four tubes. The first three tubes (11, 12, and 13) constitute the tubes for the actual test, while the last tube in the rack (14) serves as the serum control tube. Tubes 11, 12 and 13 receive, therefore, the patient's serum, the proper amount of sheep's corpuscles, dependent on hemolytic index, rising strengths of antigen, but no complement and no amboceptor. Tube 14 receives only sheep corpuscles, but no antigen.

In my technic I use 0.1 c.c. of a diluted antigen, determined by titration, in tube 11, 0.15 c.c. antigen in tube 12, and 0.2 c.c. in tube 13. In order to equalize the volume of fluid in all these tubes, I add 0.2 c.c. normal saline to tube 11, 0.15 c.c. to tube 12, 0.1 c.c. to tube 13, and 0.3 c.c. to tube 14. The tubes are then agitated and placed in the water bath for half an hour. These last four tubes are filled at the time I make the additions to the first ten and are left with them in the water bath for one-half hour for fixation of complement, the rack is then taken out and the hemolytic index computed. If the index is low, say from 1:4, I add 0.1 c.c. of sheep's blood to the last four tubes. If the index is between 5 and 7, I use 0.15 c.c. sheep's blood to the last four tubes; if between 8 and 10, I add 0.2 c.c.; if the index is over 10, I rack up ten more tubes and repeat the titration of the

natural complement and amboceptor, then I estimate that; if between 11 and 15, I use 0.25 c.c.; if between 15 and 18, I use 0.3 c.c.; and if between 18 and 20, I use 0.35 c.c. If the patient's serum has an index below 2, I regard the reaction as of doubtful value. If it is above 2, I regard it as absolute. The reaction is read off exactly as in the Wassermann, that is, inhibition or noninhibition of hemolysis. If the amount of complement or natural antishoop amboceptor is very low, we can add the proper amount of guinea pig's serum or rabbit's immune serum, ascertained by preliminary titration.

The data which we have compiled as a result of our experiences with this test are about as follows: We have approximately obtained from 15 to 20 per cent more positives with this method than with the Wassermann. We have found the Hecht-Gradwohl test strongly positive in latent syphilis where the Wassermann was negative. We have always found the Hecht-Gradwohl test positive when the Wassermann was positive. In no case out of these ten thousand records has the Wassermann ever been positive and the Hecht-Gradwohl test negative. In this connection I wish to call attention to the excellent recent publication of Kolmer<sup>15</sup> entitled "The Hecht (Gradwohl Modification) Complement Fixation Reaction in Syphilis with Special Reference to Cholesterinized Antigens." In this publication Kolmer makes the observation that he has found the modification of Hecht-Gradwohl superior to the Wassermann, particularly in treated cases, that he has found the Hecht-Gradwohl present in approximately 16 per cent more cases than the Wassermann. He makes the statement, however, that he has through possibly manipulative error found some cases with positive Wassermans and negative Hecht-Gradwohl. He also claims that in 4 per cent of the cases examined he found positives which he believed were not specific. He states that my reaction yielded 12 per cent more true positive reactions than the Wassermann with cholesterinized extract and when conducting the Wassermann reaction with an alcoholic extract of syphilitic liver, the Hecht-Gradwohl yielded about 26 per cent more true positive reactions and about 18 per cent more reactions than results with an extract of acetone-insoluble lipoid in the Wassermann system. I wish to emphasize at this point that while Kolmer obtained results which are strikingly like my own in point of percentage, his own statement that his results with a positive Wassermann and negative Hecht-Gradwohl were possibly due to

manipulative error is possibly correct; more than this, he did not follow my exact technic; to-wit, he used but five tubes in estimating the hemolytic index which in my experience will not give that exactitude of results which I claim for this test. The "skipping" of the tubes, as he has done, is saving of time at a sacrifice of accuracy. It is this very variation in the technic which explains his failure with my method to confirm in every particular the results of my extensive experience with this test. There are sometimes unknown factors which make one of the tubes in which the hemolytic index is estimated display lack of hemolysis, and the very next two or three tubes beyond that will show complete hemolysis. I am certain had Kolmer the opportunity to personally watch my technic, he would be able to revise his observations. He calls attention, moreover, to the phenomenon of false positives called by Noguchi the "proteotropic reaction" due to the use of an active serum with crude alcoholic extracts as antigens. This phenomenon does not occur with the use of the acetone-insoluble, ether-soluble fraction of Noguchi, and it is for this reason that I have always utilized this particular antigen in the Hecht-Gradwohl test, consequently I have never had the bizarre result noted by Kolmer.

The amount of antigen used by me in this test is usually 0.1 c.c., 0.15 c.c. and 0.2 c.c. of a dilution of 1 to 20 of the acetone-insoluble, ether-soluble fraction. I find that this amount is usually from one-half to one-third the titer of that actually used in the Wassermann technic. I have found that 98 per cent of the sera tested by us showed sufficient antish sheep amboceptor and natural complement to carry out the test. Inasmuch as we usually make our tests within twenty-four hours after the withdrawal of this blood from the patient, we have not been forced to work under the hardship of loss of natural complement which ensues when blood is not examined soon after withdrawal. It is our purpose later to publish a method of preserving the natural complement in human serum indefinitely, so that the Hecht-Gradwohl test may be successfully carried out as long as one week after the withdrawal of the blood. For the present I wish to state that if blood is examined within twenty-four hours after its withdrawal, there will be sufficient natural complement left to carry out this test.

For purposes of illustration, the racks lined up for the test are shown.

The purpose of the introduction of a discussion of this test into this

paper was to show that it has succeeded often where the Wassermann has failed, and that in latent cases it will show a reaction where the Wassermann will not. I wish it to be understood that as a control over treatment, as has been emphasized by Kolmer,<sup>16</sup> Heidingsfeld,<sup>17</sup> Schmidt,<sup>18</sup> Wolbarst,<sup>19</sup> and others, the Hecht-Gradwohl is far superior to the Wassermann. The Wassermann responds often quickly to treatment and more rapidly disappears. The Hecht-Gradwohl does not. It requires a great deal of treatment to make this reaction disappear. It is therefore a far better indicator of the efficiency of treatment than the Wassermann. Heidingsfeld<sup>20</sup> states that both the Wassermann and the Hecht-Gradwohl tests are trustworthy and when combined, they are a check on each other. The Wassermann reveals the degree of early improvement, but the Hecht-Gradwohl test is usually positive long after the Wassermann is negative, and measures with much greater delicacy and precision the last traces of serological inhibition. Kolmer<sup>21</sup> states that the Hecht-Gradwohl reaction has its greatest value as a serological control in the treatment of syphilis. In his experience during treatment the Wassermann reaction with an alcoholic extract of syphilitic liver is usually extinguished first and after considerable more treatment, it is generally extinguished with a cholesterinized extract; the Hecht-Gradwohl reaction is usually last to react in a negative manner. There seems therefore to be perfect agreement among all who have had experience with this test as to its value as a means of controlling the treatment of syphilis.

The writer, however, feels that it is not only a better control over the Wassermann in treatment, but that it far surpasses the Wassermann as a diagnostic aid in many latent cases. There are innumerable records to prove this; space forbids here a catalogue of cases. This test points to the presence of syphilis where the older test fails to do so because of the better adjustment of the reagents. It has another advantage which Wassermann workers will appreciate more than can be described. I refer to the reading of the so-called "border-line" positives in the straight Wassermann technic. There are many times when the Wassermann test shows what is called a "border-line phenomenon." That means a very faint inhibition of hemolysis. This may indeed be an indication of the existence of a faint trace of syphilitic antibody or it may mean a "spurious" reaction. In such a case, the Hecht-Gradwohl yields a strongly positive or complete inhi-

bition of hemolysis if the serum is really syphilitic, and a complete hemolysis or negative if the Wassermann reaction border-line is a spurious one. This certainly definitely establishes its value, if nothing else does, for the proper interpretation of a "border-line reading" is one that has sorely tried the confidence of both serologist and clinician.

In conclusion, it may be stated that as a result of the methods of diagnosis of the primary lesion by means of the finding of the spirochete pallida in the lesion, by means of the Wassermann and the Hecht-Gradwohl reactions in blood, and the Wassermann reaction, lymphocyte count, globulin, and Lange colloidal gold test of spinal fluid, we have gone far ahead since the uncertainty of the days before 1905. We have by these tests placed the matter of the early diagnosis of syphilis within the reach of every practitioner. We have by these scientific laboratory methods given the clinician and the pathologist a true estimate of the prevalence and ravages of this disease. We have shown that with intelligent and early treatment of the most intensive nature syphilis may be controlled and the old nightmare of hereditary syphilis largely eliminated. Returning to our original opening remarks, we have proved that the Collès-Baumes law is correct, that the mother cannot contract syphilis from her syphilitic offspring because she *already* is infected; for witnesses of this we call the Wassermann and the Hecht-Gradwohl to testify. We have completely eliminated Profeta's law; here again the Wassermann reaction and the Hecht-Gradwohl have proved the case. We have proved that so-called "parasyphilis" is most malignant syphilis of the brain and spinal cord. We have proved that the latent syphilitic may be easily labeled and perhaps thereby syphilis of the viscera or nervous system may be avoided. We have uncovered this disease where before it would never have been suspected. I referred in the opening of this paper to the remarkable attention paid in the past to the subject of hereditary syphilis as opposed to the scant interest in acquired syphilis. Was this not due to the widespread transmission of syphilis from latently infected persons who did not display symptoms that were even recognized as syphilitic manifestations, and effects from which the parent subjects perhaps later on lost their lives with no thought on the part of the profession of their syphilitic nature? Is it not true today that with the proper recognition of syphilis and its better treatment, there is not nearly so much con-

genital syphilis as occurred in former days; in fact, we rather believe that the preventable phases of this disease—of which congenital lues is one—are now becoming of lesser importance. The textbooks of today are occupied largely with a review of the multitudinous aspects of acquired syphilis because by means of laboratory methods, these acquired cases are now under rigid investigation. Another remarkable reversal of form with respect to congenital syphilis must be mentioned: the results of the present treatment of those congenitally infected are far superior to the older days. The congenitalluetie did not in any manner respond so well to mercurial treatment as he does to the arsenical preparations of today. In this chapter too, therefore, our books must be rewritten.

We have a note of warning to sound even while we are lauding the great progress that we have made; namely, the finding of a positive Wassermann reaction and a Hecht-Gradwohl does not always mean that all the symptoms of all cases are due to syphilis. There may be coexisting disease besides syphilis in the presence of a positive Wassermann so that a clearing up of the Wassermann reaction and the Hecht-Gradwohl tests after adequate treatment with no clearing up of symptoms may indicate that there is something else besides the syphilitic infection to deal with. The *patient* must be treated, as well as the disease, and other diseases as well. A positive Wassermann coexisting with a cancer should not shut our eyes to the necessity of surgery for the cancer. Cardiac or renal degeneration coupled with syphilitic manifestations of other kinds should not make us forget the proper therapeutic indications. Estimation of cure of the patient is perhaps the one thing which has yet to be elaborated. Wassermann and Hecht-Gradwohl negative, time and again, spinal fluid negative, provocative negative Wassermann after salvarsan try-out; does this prove that the syphilitic is cured? Reinfection after all is still our best proof, but, of course, this is purely a proof of the *curability* of the disease; healthy progeny may or may not prove it. After all, with respect to mathematical exactitude regarding this point, have we proved our case with serological methods?

Have we by these means removed what the older writers considered the sharpest sting of syphilis, its uncertainty of cure, its liability to relapse? In a relative sense we have, but insofar as mathematical exactitude is concerned, we have no one test, no one absolute

means of estimation of complete and full "cure." To those who insist upon a proof of this kind, it must be conceded for the sake of argument that the sword of Damocles always hangs suspended over the head of any individual who has ever been infected with the spirochete of Schaudinn. We do maintain, however, that the realization of a *therapia sterilisans magna* is often achieved even though mathematical proof is not at hand to verify it. An observation of another generation of the progeny of those now being infected and treated may perhaps solve this ancient riddle.

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## THE INFLUENCE OF THE WASSERMANN TEST ON SURGERY\*

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IN every surgeon's career certain cases stand out as milestones in experience, and as signposts on surgical pathways. I cite several cases that have left lasting impressions, and that have notably influenced my surgical procedures with patients.

In 1896 while I was assistant to a noted surgeon in Philadelphia, a case of periosteal sarcoma of the lower end of the femur was referred to him for operation by a physician in a western city. The patient, a woman of 32 years, was examined, the diagnosis was accepted, and operation was advised. She declined to enter a hospital, and an adjoining room to her suite in a hotel was fitted up as an operating room. She was prepared for a high thigh amputation. She was etherized on the operating table, and the tourniquet was in place. The surgeon, a former assistant to the elder Gross, and a recognized authority on macroscopic pathology, suddenly decided that before amputating he would incise the tumorous growth to inspect its texture and to reassure himself of the correctness of the diagnosis. He incised the nodular mass, remarked its likeness to a gumma, and halted the operation. When the patient had sufficiently recovered from the incision to start constitutional treatment, an intensive course of mercury and the iodides was instituted. The growth rapidly disappeared, and in time the woman was returned to her physician for a continuance of antiluetic treatment.

In 1902 a patient came to me with a discharging sinus of the anterior wall of his chest leading down to a necrosed 5th left rib. He was a spare, wiry man of about 60 years, beginning to break physically. I made careful inquiry into his history and elicited no record of trauma, or of venereal infection, or of typhoid. He showed no con-

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stitutional evidence of syphilis or of tuberculosis. I excised the necrosed portion of the rib with generous margin. The wound healed satisfactorily, and an iron tonic was prescribed. Six weeks after operation, the patient returned improved in health, but with a tumefaction beneath the scar. Incision showed a necrotic end of the 5th rib and periosteal swelling of the adjoining 6th rib. The fragment of rib with its periosteum and cartilage, and a portion of the 6th rib with its periosteum and cartilage, were removed. The wound healed and remained so for four months. Then there was evidence of a return of the trouble, with involvement of the sternum. I decided to give the patient the therapeutic test for syphilis. He was put on mixed treatment and mercurial inunctions. The swelling subsided, the patient gained in weight and vigor, and when confronted with the evidence of responding to antisiphilitic treatment, he acknowledged that he had had a urethral chancre and syphilodermata while confined in Libby prison during the Civil War.

In 1903 I was investigating the hepatic sequelæ of amebic dysentery with a view to their early recognition and treatment. Many of these cases, however, came under observation late in the course of the disease, and I operated on some fifty cases of liver abscess. One case, a man of 25 years, appeared with symptoms that I considered typical of amebic hepatitis, with pus formation, and signs indicating adhesions underneath the outer lower liver margin. He had had a severe attack of amebic dysentery a year before admission, but his stools had since become free from amebæ. He was emaciated and sallow. His right lower chest was bulged and his liver was enlarged and quite tender along the lower border; his leucocyte count was high, and his temperature curve and pulse rate were right for operation. A Kocher incision for location of pus was disappointing in its findings. There were extensive adhesions on the upper surface of the greatly enlarged right lobe, but there was no area of bogginess. Beneath the liver there was a matted mass of neighboring organs, with new adhesions and dense fibrous bands, involving liver, gall bladder, pylorus, colon, and omentum. A prolonged dissection cleared the stomach, duodenum, gall bladder, pancreas and large bowel of focal cause. I was at a loss to explain how an amebic hepatitis, without pus formation, could be involved in such an extensive inflammatory process with neighboring viscera. The abdomen was closed. About a

week after operation a member of the staff suggested that a course of antisyphilitic treatment could do no harm, which suggestion was immediately put into effect. The rapid clearing up of the patient's symptoms, his remarkable gain in weight, his complete recovery, and his ultimate return to duty in the service, has left an indelible stamp on my memory.

These cases, epochal to me, arose before the principle of complement fixation was utilized as a diagnostic measure. It was not until 1909 that the Wassermann test came into accepted use in the Army, and then only in the larger hospitals, in one of which I was fortunate to be stationed. Since then its use has become general throughout the service, and has attained a place in laboratory diagnosis equal at least to that of the x-ray in importance. Like in x-ray work, its reliability is dependent entirely on the skillfulness of the technician and on his ability to properly interpret findings; and this interpretation must be made in the light of clinical evidence and to the exclusion of other conditions that would have a direct bearing on the case in hand. The serologist must, therefore, be an experienced man, reliable in technic, clear in his understanding as to eliminating error and in estimating clinical symptoms; and the laboratory report will have a value that is inestimable to the clinician.

With the introduction of the Wassermann test as a laboratory procedure, it was my custom to request a blood examination in surgical cases only in such cases as gave a history of infection, or of past symptoms, or of suspicious lesions which might prove to be syphilitic. It was not long, however, before I discovered that such investigation did not include all syphilitic cases that came under my care. I found, for example, certain slow-mending fractures needed serological investigation, and got definite positive findings in some cases and results under antiluetic treatment. I found that some cases of nephritis that were under treatment in preparation for surgical operation in other regions, like hernia and appendicitis, gave positive Wassermann tests and cleared up under salvarsan and mercury. I found that certain cases of diabetes with surgical requirements gave a positive test and responded to antisyphilitic treatment before operation was performed; and I found that causation in diseases of vessels, and in aneurysm associated with trauma was frequently lightened by posi-

tive Wassermanns; and that ascribed surgical lesions of the central nervous system were more frequently syphilitic than I had supposed.

I therefore began to use the Wassermann test as a routine examination in all surgical cases, this request being made to the hospital pathologist on the admission of a patient, in the same way that a routine examination of urine is requested. The result of this routine method has been invaluable in reaching diagnosis, both in obscure conditions and in cases where lesions might likely be ascribed to other causes. There are, for example, under treatment in the surgical service of this hospital, several cases of syphilitic arthritis that were sent here as cases of rheumatism; a case of ascites that was sent here for a Talma operation, a case of suspected amebic dysentery, and a case of necrosis of the tibia, all of which gave strong positive Wassermanns, and are undergoing antisyphilitic treatment. Even in cases of traumata of all kinds, including gun shot wounds, the Wassermann test is not disregarded, and proper treatment following a positive report from the laboratory has influenced the course of healing. Indeed one is astounded at the prevalence of the disease among individuals that come for surgical operations, when one sums up at the end of the year the percentage ofluetics appearing in a surgical service.

The surgeon who not having done so, will institute the practice of getting reliable Wassermann tests in all his cases as a routine practice, will have many surprises in store, as I have had, and he will get results with his cases that were denied him before making general use of this invaluable aid in the diagnosis.

As to the diagnostic value of the laboratory findings and its bearing on reaching a conclusion in the management of cases, I do not of course make use of the report as the only reliance in reaching a diagnosis of syphilis in questionable cases. The pathologist making the report, who, as before stated, to be reliable must be an experienced man, is brought into the case and goes over all of its phases with the surgeon. The clinical findings, the symptoms, and the history are weighed, and the pathologist brings his laboratory knowledge to the bedside in consultation. The lines of thought in such investigation often take surprisingly new routes—generally to the edification of the surgeon, though not infrequently obscure conditions will be discovered that will lead to new investigations and will influence or change the meaning of

the serological findings. This was particularly true in the tropics when yaws, leprosy, and latent malaria were so frequently met with.

In general, it may be stated that surgical cases appearing for operative interference, if they have syphilis, are in the later course of the disease. While untreated syphilitics the first year will give nearly 100 per cent positive Wassermanns, the ratio of positive findings will drop as the disease ages in the individual. Late visceral, bone, and central nervous system lesions will be the principal seats of involvement which the surgeon will have to ferret out, and the Wassermann test is strongly positive in 95 per cent of lesions of the viscera, in 90 per cent of lesions of the bone, and in 80 per cent of lesions of the central nervous system. It is my practice to corroborate a strongly positive test by an additional test, and not to accept a weakly positive test, or a series of such findings, as final in determining active treatment, in the absence of history or clinical evidence being elicited. Also, a negative test is not considered as disproving the presence of syphilis, especially if there is a questionable history of suspicious evidence of latent disease, for the reaction may vary at intervals in untreated cases. Three negative tests in as many months in such cases, reinforced by a negative provocative Wassermann, and by a negative spinal fluid test if there is a history of syphilis, or if there are clinical manifestations of involvement of the central nervous system, are accepted as conclusive of the absence of syphilis.

## SYPHILIS OF THE DUODENUM\*

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THE clinical diagnosis of syphilis of the intestine has for many years been exceedingly difficult, for with the means of diagnosis existing some years ago, it was impossible to localize the seat of the pathological changes; furthermore, unless the patient presented a history of infection, or showed characteristic external signs, the possibility of syphilis was excluded. Whatever knowledge then possessed was supplied by the pathologists rather than by the clinician. Generally the nature of an intestinal lesion being syphilitic was discovered accidentally post-mortem.

With the valuable aid rendered at present by our modern efficient methods of diagnosis, especially the Wassermann reaction and the roentgen ray, more cases of intestinal syphilis should be recognized during the earlier stages, before permanent destructive changes have occurred.

In Stolper's<sup>1</sup> statistics of 61 cases of visceral lues, there were nine instances involving the stomach, and twelve involving the intestines. In the combined statistics of Chiari and Stolper<sup>2</sup> there were 18 cases of intestinal lues out of 160 of visceral lues. Fränkel<sup>3</sup> reports three cases of syphilis of the small intestines, these were not diagnosed during life, but were discovered at postmortem examination. The diagnosis of the first, made antemortem, was acute intestinal obstruction; the second, carcinoma of the intestines; and the last, severe secondary anemia resulting from profuse intestinal hemorrhages.

Gross<sup>4</sup> describes the pathological changes, especially the resulting stenosis, in two cases of intestinal syphilis. In Buttner's case of congenital syphilis of the stomach, there was also an involvement of the intestines. Fränkel demonstrated the spirochete pallida in a case of congenital intestinal syphilis. Other cases have been described by Blackmore,<sup>5</sup> Oser,<sup>6</sup> Klebs,<sup>7</sup> Birch-Hirschfeld,<sup>8</sup> Guttman,<sup>9</sup> Kohn,<sup>10</sup> and Homen.<sup>11</sup>

Syphilis may occur as a true intestinal disease without a genital

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lesion or any outward sign. A negative history of infection is obtained in (a) hereditary lues, (b) those infected during infancy by a wet nurse or by other extragenital channels unknown to the patient, (c) when the source of infection and initial lesion remain occult.

With a history of sterility, abortions, stillbirths, or death of a child shortly after birth, syphilis should be considered as a possible cause. Although the Hutchinson triad may be absent in hereditary syphilis, yet if the patient denies infection, an examination of the children should not be omitted, for they may reveal an interstitial keratitis, labyrinth affection, or the characteristic notched teeth.

Syphilis of the intestinal tract may develop within the first years of infection, though in hereditary lues the symptoms have been known to manifest themselves after a lapse of twenty-five years.

The fundamental anatomical changes in duodenal syphilis are identical with those found in syphilis of the stomach: (a) gummatous plaques, (b) gummatous ulcers, (c) hyperplasia, and (d) cicatricial contraction. In syphilitic stenosis of the pylorus, there is a diffuse cellular thickening of all layers, which may involve the entire circumference. It has been mistaken for a carcinoma.

Gummata are the most characteristic growths found in intestinal lues: the number is various, the size may vary from a few centimeters to the size of the palm of the hand. They are generally dirty white or yellow in color, with hard, well defined borders. A fresh gumma is more vascular than an old one, since the usual obliterating endarteritis and endophlebitis have not reached an advanced stage. Through the disintegration of the gumma, there occur ulcers of varying size and depth. According to Neuman,<sup>12</sup> the most frequent site of the gummatous changes are found in the jejunum and ileum, though they have been found as high up as the duodenum.

An encircling of the intestines by an ulcer may result in stenosis after cicatricial contraction has occurred. (Oser,<sup>6</sup> Fränkel<sup>3</sup>). Gummata have a tendency to terminate either in fibrous tissue or undergo fatty degeneration and necrosis.

The symptoms of syphilis of the small intestines are very diverse. First and foremost, they may result from the general inanition and anemia attendant on syphilis, and, as in many other constitutional diseases, are not especially characteristic. Abdominal pain, and tenderness more severe at night, distention, tumor, diarrhea, at times alter-



Fig. 1.—Before treatment.







Fig. 2.—After treatment.



nating with constipation, and melena are the commonest findings found in the reported cases—symptoms refractory under ordinary treatment, but readily controlled by specific treatment.

The prognosis naturally depends upon an early recognition of the condition.

#### CASE REPORT

An American widow, age 37, gives following history: Married 13 years ago. One year later began to have gnawing epigastric pains, radiating to the right for a short distance, which came on several hours after meals; nausea, no vomiting, no pyrosis; eructation of gas often relieved the pain. There was often an accompanying feeling of hunger and faintness. Bowels were constipated. This attack subsided without any treatment; however, other similar attacks followed at various intervals.

Eleven years ago, after eight months of pregnancy, patient gave birth to a child that died the following day. Patient was later informed that child showed definite signs of syphilis. Mixed treatment was taken for a brief period. Three years ago her husband developed paresis showing a positive Wassermann reaction of the blood serum and spinal fluid. The patient's blood serum was also repeatedly strongly positive. Both were given a vigorous course of salvarsan and mercury. Husband died eighteen months ago. The patient's Wassermann was then reported negative. During the antisyphilitic treatment, there were no digestive disturbances.

Four months ago, attacks recurred with increasing frequency and severity. Appetite fair. Sleep disturbed by epigastric pain. There has been slight loss of weight since the onset of recent illness.

Physical examination shows a fairly nourished woman weighing 120 pounds. Skin and mucous membranes are pale. Over the left cervical region an enlarged gland the size of a walnut is palpable. The findings of the heart and lungs are negative.

Abdominal examination reveals slight distention, no rigidity. There is tenderness over the epigastrium on pressure. In the right hypochondrium a hard irregular mass about two inches in length is palpable; it is neither movable on palpation nor respiration. Liver and spleen not enlarged. No ascites. Extremities and reflexes normal. Pupils react promptly.

Temperature normal. Pulse 90. Systolic blood pressure 120, dias-

tolie 85. Urine is scanty. Specific gravity 1035, and excepting for an excess of indican and urates the findings are negative. Blood: hemoglobin 70 per cent. Wassermann reaction strongly positive. Stool: occult blood, negative.

The fluoroscopic examination by Dr. Brandenburg shows a rapidly filling stomach which is enlarged, the greater curvature being about two inches below umbilicus. The peristaltic waves are rapid and of moderate depth. Within a few minutes the post-pyloric region is visualized, showing a narrow irregular filling defect which persists. There is a disfigured duodenal cap. There was no six hour residue seen.

Antisymphilitic treatment was immediately started consisting of an intramuscular injection of salicylate of mercury every five days, also fifteen drops of a saturated solution of potassium iodide three times daily administered by mouth which was well tolerated. Within a brief period there was distinct improvement of subjective symptoms, and at present, after two months of treatment, the patient is entirely free of abdominal pain, tenderness, or any digestive disturbance. The rapid, favorable symptomatic results of the antiluetic treatment in this case is surprising, since the serologic findings are unchanged. Moreover there is a distinct broadening of the duodenal shadow on repeated observation. Furthermore there is a very perceptible diminution in the size of the tumor.

A diagnosis of duodenal syphilis seems to be justified in this case for the following reasons:

1. History of onset one year after marriage, the birth of a syphilitic child; husband died of paresis. Both Wassermann reaction and symptoms cleared up previously under antiluetic therapy.

2. Presence of a hard irregular mass in the right hypochondrium.

3. Roentgen signs which show decisive evidence of post-pyloric pathology.

4. Positive Wassermann reaction.

5. The marked improvement under antiluetic therapy, the patient stating that she was entirely free of abdominal pain and tenderness. The diminution in the size of the tumor.

In conclusion, I wish to quote Carman,<sup>13</sup> who says that a correlation of all the evidences from all sources may maintain a diagnosis as conclusively as many other diagnoses which are freely accepted.

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## EXPERIMENTAL SYPHILIS PRODUCED THROUGH LOCAL APPLICATIONS TO MUCOUS MEMBRANES\*

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(Received for publication, March 10, 1917)

DIFFERENT writers have called attention on various occasions to the observation that *Treponema pallidum* may, under certain conditions, exist for a number of hours when removed from its normal habitat in an infected individual. It would seem, therefore, that it should find much better temporary quarters if accidentally transferred to a moist mucous membrane, where in addition to the body secretions, it would also have the advantage of body heat. In such case it is not difficult to comprehend how the organism might live for a number of hours and even undergo an increase in numbers; the conditions being in some degree similar to that confronting the free *Treponema* in mucous patches.

It has been frequently stated and quite generally accepted that *Treponema pallidum* can not gain entrance to the human body through the unbroken skin or mucous membrane. So far as I know, this statement is not founded upon any scientific basis, and has never been proved or disproved. I can see no reason why this organism should not pass into one of the squamous cells of the mucous membrane as into cells of the liver or pancreas or other organ, and especially so where desquamation has just taken place. Possibly some such thing takes place in the initial lesion occasionally noted in the eye or nose of a physician as a result of the coughing of infective material by a patient. It would seem possible that it might gain entrance to a duct of one of the many glands present and from there make its way either through or between the lining cells as it does in other parts of the body. Such a possibility should be considered in explaining the relative frequency of chancres of the tonsils or of the lining membrane of a redundant foreskin. The reverse of this process would explain the presence of the organism in the spinal fluid.

\*From the Department of Pathology, Army Medical School, Washington, D. C., continuing certain investigations initiated by Major H. J. Nichols, Medical Corps, U. S. Army.

It does not seem possible that such a process would take place through the epithelial cells of the unbroken skin as the epithelial cells are of a different character and the continuous moisture necessary for the existence of the organism is ordinarily lacking. It is well established that the nonmotile staphylococci and streptococci frequently gain entrance by means of the hair follicles of the skin, and that having once gained entrance, the conditions are favorable for germ activity. It seems very improbable that this extremely delicate organism should gain entrance in such a manner, but this paper is intended to suggest possibilities as well as probabilities. At this point one is confronted with the difficulty of determining when the surface of the skin or mucous membrane may be designated as unbroken. I think it will be granted that the too strenuous use of the nail brush and nail file upon a tender skin may result in minute abrasions which would only be evident when subject to magnification or the application of certain irritating fluids. The use of solutions of bichloride of mercury upon some skins will have the same result. These breaks in the skin might well serve while fresh, as an avenue of entrance of such an infecting organism. I believe also that as a result of the trauma to which the hands are constantly subjected, minute abrasions are of frequent occurrence. Such a method of transmission is of importance to the physician as a matter of possibility, if not of probability.

Due to the constant desquamation of the external layer of cells of the mucous membranes, I think it would be rather a difficult matter to state when it is absolutely unbroken if it ever is, strictly speaking, in such a condition.

If the above premises are correct, it would seem, therefore, that the apparently normal surface of the mucous membranes and the skin of the hands and the shaven face are not necessarily at all times intact, and if we accept the mucous glands and go to the extreme of considering the hair follicles as possible avenues of approach, they are at all times vulnerable.

On account of practical difficulties, the study of the disease in man offers little toward the solution of the problem, and we are compelled to turn to animal experiment. With this idea in view, experiments with a small series of eight animals were started on April 18, 1916. These rabbits were examined carefully and, as well as

could be determined with a hand glass, there were no abrasions at the places where the syphilitic emulsion was applied. A very rich emulsion of *Treponema pallidum* was prepared from the testicular juice of strains No. 5 and No. 11 previously described by Nichols and by me.<sup>2</sup> This emulsion was then carefully dropped upon the mucous membranes of the rabbits as follows, after which the animals were placed temporarily in individual cages:

No. 1.—Female. Both eyes and mouth. Negative result.

No. 2.—Female. Both eyes and mouth. Negative result.

No. 3.—Female. Both eyes, nose, and vagina. At the end of fifty-five days, a slight nasal discharge was observed which later increased in quantity and at the same time the breathing of the animal became much interfered with, due to a partial closure of the nostrils. No ulcer or tumor could be observed. The eyes and vagina remained apparently normal. It was not possible to demonstrate any treponemata by dark-field examination. The rabbit became emaciated, and finally died before it was possible to establish a diagnosis.

No. 4.—Male. Both eyes and nose. Negative result as was shown by the subsequent successful testicular inoculation with the No. 5 strain.

No. 5.—Male. Both eyes, nose, and left groin. Negative result. Died at

No. 6.—Male. Penis and inside of prepuce and on scrotum. Negative result. the end of fifty-five days.

No. 7.—Male. Nose and both sides of scrotum. Negative result.

No. 8.—Female. Both eyes, nose, and vagina. On June 1, 1916, or after an interval of forty-three days, there was evident a vaginal ulcer, the secretions from which showed by dark-field examination, the presence of many characteristic organisms and which was transferred to another rabbit and resulted in a typical No. 5 testicular lesion.

Rabbits Nos. 1, 2, 4, 5, 6, and 7 may for the purposes of this paper, be accepted as negative results. Rabbit No. 3 may be classed as doubtful. The nasal mucous lesions were similar to those noted in the No. 5 strain.<sup>2</sup> Uhlenhuth and Mulzer<sup>3</sup> describe a similar condition in some of the syphilitic rabbits studied by them. It is not always easy to find treponemata in this nasal discharge, and when found they are few in numbers and generally to be found only after prolonged search. The subsequent course of this rabbit is about what would be expected if this condition were syphilitic. It is unfortunate that this animal did not live long enough to establish a diagnosis.

Rabbit No. 8 may be accepted as a positive result.

It is not intended to establish any percentages from this small series but simply to show that it is possible to transmit syphilis



through the mere application of infectious material to the apparently normal mucous membrane. It is believed that the same result may be obtained through minute fresh abrasions upon the surface of the skin. The possibility of entrance through the hair follicles of the skin might well be the subject of further investigation.

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# Abstract of Current Syphilis Literature

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WM. H. DEADERICK, M.D., EDITOR

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THE SYPHILIS PROBLEM AMONG CONFINED CRIMINALS.—Eugene N. Boudreau, Auburn. *Medical Record*, December 2, 1916.

Eighteen and eighty-five hundredths per cent of the males, and thirty-three and eighty-five hundredths per cent of the females of Auburn Prison are found to have given a positive Wassermann. Seven and five-tenths per cent of all admissions are potential sufferers from paresis or tabes, or some other form of nervous syphilis, and, consequently, future wards of the state. It would cost the State of New York approximately \$9,000 a year to treat properly all cases of syphilis at Auburn Prison. History, glandular enlargement, and physical findings in general, are further proved to be lacking as evidence of the present syphilis. Epitrochlear gland enlargement is not pathognomonic of syphilis.

SOME PHASES OF EXPERIMENTAL SYPHILIS WITH SPECIAL REFERENCE TO THE QUESTION OF STRAINS.—Mathew A. Reasoner, Washington, D. C. *Journal of the American Medical Association*, 1916, vol. lxvii, p. 1797.

Reasoner has been able to demonstrate to his satisfaction fixed differences in various strains of syphilis as studied in the rabbit. Choroiditis and chorioretinitis have been observed in rabbits inoculated with two different strains of nervous syphilis, and in one strain whose characteristics are not known. Interstitial keratitis and pericorneal injection are frequent manifestations of generalization in some of the various strains observed. The author agrees with Noguchi that the nervous system of the rabbit is resistant to syphilitic infection. From eight injections of human spinal fluid only two successful inoculations were obtained. No morphologic differences in the various strains studied could be discovered, and no permanent alterations in the characteristics of the strains were observed following the prolonged growth and repeated transfers in the rabbit.

THE INFLUENCE OF CARBOHYDRATES ON THE CULTIVATION OF SPIROCHETES.—Seinai Akatsu, New York. The Journal of Experimental Medicine, 1917, vol. xxv, p. 379.

In media containing glycogen and glucose, *Treponema microdentium* did not grow as vigorously as in other sugar media, and an earlier degeneration set in. One strain of the pallidum and the calygyrum and mocosum showed a poor growth in the glycogen medium. Similarly, there was little growth in the second transfer of these spirochetes in the glucose medium. The growth of the spirochetes in the media containing carbohydrates other than those just mentioned was generally good, and no difference could be distinguished between these and the other cultures without any carbohydrate. The only phenomenon which might be interpreted as indicating a favorable influence of these media upon growth was the abundant growth of the mocosum, which showed uniform length, regular curves, and active motility somewhat better than in the sugar-free medium. The height of acidity was found in the cultures containing glycogen and glucose in the microdentium amounting to 0.1 n 4.8 c.c. for 10 c.c. of the fluid culture. In the other sugar media the acidity varied between 0.1 n 3.2 c.c. for the same amount. In the control cultures, the acidity fluctuated from 0.1 n 0.8 c.c. to 0.1 n 2 c.c. There was no visible alteration in the appearance of the media after the spirochetes had grown for three or four weeks. In the case of *Treponema microdentium*, a slight opalescence developed in the glycogen and glucose media after several weeks' standing, but there was no precipitation of the proteins of the culture media. There was no unusual morphological change in the spirochetes grown in the media containing any of the carbohydrates employed. The only phenomena which should be mentioned are, (a) the frequent presence of the terminal appendages (or projections) in the refringens and in most of the pallidum strains, and (b) the appearance of minute, refractile spherical bodies along the side of the spirochetes in the microdentium cultivated in the glucose or glycogen media. Judging from the earlier degeneration of the species in the above mentioned media, these peculiar bodies may be interpreted as indicating a phase of plasmoptysis associated with the unfavorable surroundings prior to degeneration. Experimental evidence was not found for considering these spherules as a resistant or spore form of the spirochete.

DRUG-FASTNESS OF SPIROCHETES TO ARSENIC, MERCURIAL, AND IODIDE COMPOUNDS IN VITRO.—Seinai Akatsu and Hideyo Noguchi, New York. The Journal of Experimental Medicine, vol. xxv, No. 3, p. 361.

*Treponema pallidum* and *Treponema microdentium* have, within three to four months, increased their tolerance to salvarsan and neosalvarsan to five and one-half times their original mark. With Spiro-

chete refringens the increase was about three times. Against the action of bichloride of mercury the amount of increased tolerance of *Treponema pallidum* was about 35 to 70 times the original, while that of *Treponema microdentium* was about ten times as much and was reached within ten weeks. Spirochete refringens resisted thirty times the original dose. There was an unmistakable increase of resistance of these spirochetes to the action of the iodine-iodide solution (Lugol's solution) when they were grown for several generations in fluid media containing the iodine solution, but the rate of increase between the initial and the acquired tolerance was slight. In general, the addition of Lugol's solution to fluid media has a weak inhibitory influence upon the growth of the spirochetes, requiring for the total suppression of growth a quantity of over 0.7 c.c. to 5 c.c. of the culture media. The tolerance reached was for about three times that amount. A similar tolerance phenomenon has not been established when employing a solid instead of a fluid medium containing the drugs. No explanation is offered except a suggestion that the drugs held in the agar do not enter into combination with certain tissue constituents of the medium as they are able to do with tissue elements in fluid media. This may be a factor necessary for inducing drug tolerance in these organisms *in vitro*. The increased drug-fastness has a limit beyond which no further advance can be made. This limit varies with different species of spirochetes. The acquired drug-fastness *in vitro* gradually disappears when the spirochetes are cultivated again in the drug-free media for several generations.

REPORT OF A SERIES OF SIXTY-ONE EXTRAGENITAL CHANCRES.—H. N. Cole, Cleveland. *Journal of the American Medical Association*, 1916, vol. lxvii, p. 1805.

The author reports sixty-one cases from his private practice and clinics. The ages vary from two months to sixty-five years. Twenty-nine patients were from twenty to thirty years of age; thirty-three were married and twenty-eight single. Forty-three cases occurred on the lips, upon the lower in thirty-seven, upper, seven, and not recorded, four cases; three cases appeared upon the tonsil; tongue, one; hand, ten; neck, one; jaw, one; abdomen, one; nipples, one. Bites were responsible in four cases; kissing in nine, and the barber shop in two cases. Late diagnoses occurred thirty-seven times in the series of sixty-one cases. In the differential diagnoses, one must keep especially in mind the gumma and the carcinoma. This applies particularly to the lip. In any persistent sore, no matter how trivial, and no matter what its location may be, the extragenital chancre should be ruled out in making the diagnosis. The prognosis of extragenital chancre, like that of all syphilis, provided proper and sufficient treatment is carried out, is good.

**THE DYSCHROMIAS OF SYPHILIS.**—Richard L. Sutton, Kansas City. *Journal of the American Medical Association*, 1916, vol. lxvii, p. 1913.

Judging from the results of the work of other investigators, as well as from his own experience in the cases reported, Sutton believes that the pigment matter is entirely a product of epidermal metamorphosis, and that the plasma cells and connective tissue cells have little or nothing to do with its formation. The fact that in some instances repigmentation occurs following the development of leukodermatous areas would indicate that in at least a certain percentage of cases the cellular changes are such that it is possible for the pigment production to occur again. The treatment of hyperpigmentation due to syphilis is that of chloasma and similar disorders.

**A CRITICAL STUDY OF ONE HUNDRED AND TWENTY CASES OF LATE SYPHILIS.**—Udo J. Wile and Joseph A. Elliott, Ann Arbor. *Journal of the American Medical Association*, 1916, vol. lxvii, p. 1917.

By far overshadowing all other causes of the appearance of late syphilitic sequelæ, the lack of, or inefficiency of, treatment during the early period stands out as the most important factor. The inefficiency of treatment by the ingestion of pills is suggested by the fact that in those cases in which treatment was given, the larger number had been treated in this fashion. The tendency for late sequelæ to appear increased up to the fourth year, which represents a fastigium after which there is a decrease in the probability. That no latent untreated cases are immune is suggested by the lapse of forty-four years after infection in one of the authors' cases. Trauma probably plays a smaller role in the production of active syphilis during the period of latency than is generally supposed. Where it occurs it is likely to influence the appearance of gummatous lesion in and around the skeletal structures. Intensive treatment, as accepted by modern methods (salvarsan and thorough mercurialization during the early months) is protective in the larger percentage of cases. In treated cases the occurrence of late sequelæ, except for isolated and exceptional cases, must be regarded as an indictment against the method of treatment.

**SYPHILIS OF THE STOMACH: CLINICAL AND ROENTGENOLOGICAL STUDY, WITH REPORT OF TWENTY-THREE CASES.**—George B. Eusterman, Rochester, Minn. *American Journal of the Medical Sciences*, 1917, vol. cliii, p. 21.

Syphilis of the stomach though rare, is not as frequent as is generally supposed. The aid of the Wassermann-Noguchi and roentgen rays is necessary to establish the presence and the specificity of the

lesion. The diagnosis is based on a history of infection and consistently positive Wassermann reaction, indisputable evidence of a gross gastric lesion and,—excluding cases showing irreparable extensive disease,—permanent cure by purely antisymphilite measures. The diagnosis is often accidental. The possibility of syphilis should be considered in every atypical case, or in those not responding to ordinary methods of medical management. The symptomatology, which is fairly characteristic of gastric syphilis, in view of the cases reported, is suggestive of benign gastric ulcer. The gastric chemistry and roentgen findings rather suggest carcinoma. The average age of patients with acquired syphilis of the stomach is about thirty-five; the duration of the complaint averages three years. In most instances the condition is characterized by initial intermittent course, followed soon by continuous symptoms associated with epigastric pain of variable degree felt shortly after taking food, and not relieved by food or alkalis. From the outset, there is a tendency toward emesis, a variable degree of flatulency, good appetite, infrequency of hemorrhage, and palpable tumor, diffuse abdominal resistance, a progressive course and marked loss in weight without cachexia. Results from instancespecific treatment are encouraging in all but very advanced cases. Surgical interference is indicated in certain cases. Early diagnosis and intensive treatment invariably result in symptomatic cure and structural improvement.

SYPHILIS AS A FACTOR IN THE PRODUCTION OF CARDIO-VASCULAR-RENAL DISEASES.—Douglas Vander-Hoof, Richmond. *Southern Medical Journal*, 1917, vol. x, p. 100.

Syphilitic arteritis involves especially the aorta, the cerebral, pulmonary, subclavian, femoral and popliteal arteries. The most common vascular lesion of syphilis is undoubtedly the specific inflammatory disease of the aorta. The early symptoms and signs of syphilitic aortitis, in addition to a positive Wassermann reaction, are precordial pain, slight dyspnea, attacks of paroxysmal dyspnea and angina pectoris, cardiac hypertrophy, increased pulsation of the vessels of the neck and the physical and roentgenographic signs of dilation of the aorta. Later in the disease the condition is generally made apparent by the signs due to aneurysm of sclerotic aortic valvulitis. Syphilitic disease of the innominate, carotid, and subclavian arteries may be attended by symptoms simulating intermittent claudication of the lower extremities, together with weakness, radiating pains, and sensory disturbances. Periodic or continuous headache, often with vertigo, is said to accompany involvement of the left carotid artery. When the coronary arteries are the seat of the disease, the attacks are anginal in character. In spite of the isolated cures and the occasional brilliant recoveries of the syphilitic cardiopath on specific treatment, the disease too often pursues a relentless course to a fatal termination.

Such being the case, physicians must appreciate the serious responsibility of the treatment of early syphilis in the wisest manner possible.

**SYPHILITIC BONE AND JOINT LESIONS SIMULATING TUBERCULOSIS.**—Arthur L. Fisher, San Francisco. *Journal of the American Medical Association*, 1917, vol. lxxvii, p. 366.

The consideration of these cases brings up several interesting questions: Why do we get so many negative Wassermann reactions in bone syphilis? The percentage is believed to be at least ten per cent. Is it because of the chronicity of the disease, and the lack of ambocceptors in the blood, not sufficient being set free to bind the complement? In a manner, it is perhaps, somewhat comparable to the fact that in a chronic pyogenic abscess there is no increased leucocytosis. Another point that these cases emphasize is that fixation of a syphilitic joint neither gives relief nor aids in a restitution of the parts to normal. Another point is the large proportion of children in these cases, eight out of eighteen, quite a contrast to the ordinary teaching that syphilitic joints are not common in childhood. Another question that comes up is what we are to consider as the most reliable test of syphilis. To the author's mind, it is unquestionably the therapeutic test, and lastly the question of the therapeutic test as a diagnostic method. This should never, or almost never, be omitted in trying to arrive at a conclusion concerning the nature of a chronic process in and about a joint. Exception may be taken to this, but in the present state of our knowledge it seems to be the best test we have for syphilis, and without it one is never sure of a diagnosis.

**CARDIAC SYPHILIS.**—Thomas E. Satterthwaite, New York. *Therapeutic Gazette*, 1917, vol. xxxiii, p. 5.

Cardiac syphilis is more common than has been supposed. Like syphilis of the lungs, it exists, and the physician who fails to appreciate either of them falls short of his duties as a practitioner of medicine. In fact, neither heart nor lungs should be examined without always holding in view the possibility of syphilis as the cause of the disease. Where it may not be possible to make a positive diagnosis, a probable one can be reached. Cardiac syphilis is an insidious disease, and its manifestations are neither pronounced nor distinctive. A cure may be possible, while relief is probable, if the lesion is not too far advanced. Treatment consists in the use of salvarsan, the iodide, and mercurials; and if there has been a positive Wassermann, treatment should be continued until a negative is obtained. Afterwards, the treatment should be along the line of therapeusis in other cardiac affections. It must, however, be borne in mind that there are some dangers connected with the use of salvarsan, especially if injected intravenously.

SYPHILIS OF THE BLADDER.—Theodore Baker, Pittsburgh. *Surgery, Gynecology and Obstetrics*, 1917, vol. xxii, p. 187.

Symptoms of syphilis of the bladder present no characteristic evidences which would at once arouse suspicion. In a majority of cases there is a painful, frequent micturition, accompanied at times by a terminal hematuria of various degrees. In the tertiary stage, hematuria is most always present. One of the striking features of most of the cases is the extreme sensitiveness of the bladder to the solutions introduced for cystoscopic examination. The urine may show nothing except a few red blood cells and some pavement epithelium in the secondary stage; or it may be more or less murky, due chiefly to red blood cells, mucus and epithelium, with a relatively small proportion of pus cells. In the tertiary stage the urine contains a larger amount of blood, but unless there has been some secondary infection, there is here also a relatively small amount of pus. Bacteria are characteristically absent except in cases of secondary infection with the usual benign or pyogenic organisms. There has been no case reported where the spirochete was found in the urine. Syphilis of the bladder is seen more commonly in the tertiary stage, the lesion consisting of ulcers, tumors, or both; but in the late secondary stage and in the tertiary stage, hyperemia, either diffuse or in patches, is constant. One should bear in mind that painless hematuria of constant onset may be due to well developed tertiary lesions, and in all such cases cystoscopy should be insisted upon.

SYPHILITIC DISEASE OF THE THYMUS IN INFANTS AND THE MODE OF ORIGIN OF THE DUBOIS ABSCESES.—Jean Oliver, San Francisco. *American Journal of Diseases of Children*, 1917, vol. xiii, p. 158.

This case occurred in an Italian girl baby six weeks of age. On examination, two large blebs were found in the abdomen, rhagades at the mouth, a serosanguineous discharge from the nose, and edema of the hands and wrists. The urine showed a heavy cloud of albumin, many granular casts, and a few red blood cells. Though no syphilitic history could be obtained from the parents, the baby's Wassermann proved positive. The child was placed on mercurial treatment, but five days after admission died with signs of pneumonia. The pathologic findings in the case showed a thymus in which cysts were present. These cysts had arisen by the cystic dilatation and coalescence of the Hassall bodies. Along with this degeneration of the Hassall bodies was an equally important hypertrophy of the reticular epithelium and the new formation of concentric corpuscles, for without these progressive changes, it is doubtful whether the cystic cavities could have arisen.



STUDIES OF THE STOMACH IN SYPHILIS.—Franklin W. White, Boston.  
Boston Medical and Surgical Journal, 1917, vol. clxxvi, p. 11.

In a group of six hundred cases of syphilis with strongly positive Wassermann reaction were found forty-four with prominent stomach symptoms, after excluding patients with hepatic cirrhosis, gumma of the liver, nephritis and tabes. In thirty-five cases no definite lesions of the stomach were proved. In nine actual syphilitic or coincident lesions were found ulcer, gumma, or cancer. There are no characteristic symptoms of syphilis of the stomach; they most times resemble those of catarrh, ulcer or growth with or without obstruction of the pylorus. Pain is common; gross hemorrhage is infrequent, possibly because of obliterative endarteritis. In the cases without organic lesion of the stomach the gastric secretion has proved normal in the majority and below normal or absent in twenty per cent. The x-ray has proved of great value in locating the lesions exactly and following their change under treatment accurately. In seven cases with stomach lesions, omitting the two cancer cases, three are well and four greatly improved. In this group there were gains in weight of fifteen to fifty-two pounds with an average gain of thirty-one pounds.

DIABETES MELLITUS AND SYPHILIS.—Joseph H. Barach, Pittsburgh.  
Boston Medical and Surgical Journal, 1917, vol. clxxii, p. 58.

The author has treated during the last two and one-half years thirty-one cases of diabetes, of which three were primary cases of syphilis. Out of the twenty-eight remaining cases, one case, a physician, became infected with syphilis seventeen years ago and now has a strongly positive Wassermann. Another case was that of a man whose wife had syphilis and was treated for ten years, and the other, a woman, was the wife of a parietic, and herself gave evidence of a syphilitic infection. His observation in fifteen diabetics, some of them having severe acidosis, showed no positive Wassermans in the absence of syphilis. It seems possible that conjugal diabetes may be the result of conjugal syphilis.

SYPHILIS OF THE GENITOURINARY ORGANS.—S. William Schapira, New York. New York Medical Journal, 1917, vol. cv, p. 206.

Syphilis of the kidney is congenital or acquired and occurs in the secondary and tertiary stages. The lesion most often found is a chronic interstitial process, less often a chronic parenchymatous nephritis. Gumma is rare and occurs only in the late tertiary stage. Amyloid nephritis is often found with syphilis. The symptoms of chronic interstitial and chronic parenchymatous nephritis do not vary with the cause. Syphilis of the bladder is not often seen. In the secondary stage it appears as an acute or chronic cystitis, with frequent, painful urination and pyuria. In the tertiary stage we find the gum-

mata which appear as papillomatous masses or as nodules covered with ulcerated mucous membrane and ulcers with thick infiltrated edges and grayish bases. The diagnosis is made by excluding other causes, by the history of syphilis, by cystoscopic examinations, and by the presence of other specific lesions. Syphilis of the vasa deferentia, the seminal vesicles, and the prostate is very rare indeed, and is very rarely recognized. Syphilitic epididymitis is uncommon compared to gonorrheal or tuberculous epididymitis. It occurs in secondary syphilis as a subacute or chronic inflammation which begins in the globus major or head of the epididymis and spreads downward, but rarely extends to the globus minor. The enlargement is hard, painless with a sharp edge and feels like a helmet fitted over the testicle. The condition is usually unilateral. Syphilitic orchitis is not at all uncommon. It usually occurs after the second year of the disease, but in rare instances is seen as early as four or five months after the appearance of the initial lesion. The pathological change is either a diffuse or a gummatous formation. Physical examination shows the skin to be normal, the testicle is enlarged, but not to more than twice its normal diameter. The testicle is hard like wood, smooth, and is insensitive.

**SYPHILIS OF LONG BONES.**—Isidore Cohn, New Orleans. *Urologic and Cutaneous Review*, 1917, vol. xxi, p. 129.

Syphilitic bone lesions are not rare. Persistent pain along the shaft of a long bone, in the absence of manifestations of acute osteomyelitis, is suggestive of syphilis as a possible causative factor. Trauma is often a provocative factor in the development of this lesion. The type of bone lesion varies. Repair takes place so completely at times that at a later date it is impossible to tell that a previous lesion existed. The pain is readily relieved by proper antisyphilitic measures.

**BILATERAL CHARCOT HIPS, OCCURRING SIMULTANEOUSLY.**—S. J. Wolf-  
ermann, Fort Smith, Arkansas. *Journal of the American Medical Association*, 1916, vol. lxvii, p. 1590.

Wolfemann reports a case in a white man, age forty-two, who had a chancre in 1891 which was not followed by noticeable secondaries. His health was excellent until the fall of 1912, when he began to have rheumatic pains below the knees, occurring only at night. These occurred intermittently for about one year. During the winter of 1914 he had another attack lasting about one month. In the summer of 1915 the pains reappeared, and in September, 1915, shooting pains started in the right thigh, which swelled to twice its normal size, but at no time did he have any fever, chill, or any pain or soreness about the hip. When examined November 3, 1915, he was unable to walk or stand erect. The knee jerks were lost, and an Argyll-Robertson pupil was present. Roentgenograms showed that the heads and necks of both femurs were gone. Some improvement was made under treatment with mercury, iodides, and arsenic.

REPORT OF A CASE OF TABETIC OCULAR CRISIS.—J. C. Mitchell, St. Paul. *Journal of the American Medical Association*, 1916, vol. lxvii, p. 1936.

The patient, a male, aged forty-two, gave a typical history of tabes, the serological and clinical findings being those most commonly found in tabes; eyegrounds showed double primary atrophy. The patient complained of attacks of sharp stabbing pains in the left eye coming on at irregular intervals and lasting several seconds. During these attacks he saw momentary flashes of light before the affected eye, and also felt irritation in the eye resembling that caused by a hair. Three weeks later he gave the following account: "Yesterday morning on awakening, my left eye felt as though it had swollen the size of a baseball." A few weeks later the patient had numbness and stiffness on the left side of the face lasting from several minutes to several hours. The patient died a few months later.

HEREDITARY SYPHILIS AS A CAUSE OF CHRONIC INVALIDISM.—Henry F. Stoll, Hartford, Conn. *Journal of the American Medical Association*, 1916, vol. lxvii, p. 1885.

When pregnancy results in a syphilitic, one of several things may happen. (1) The fetus dies and abortion or stillbirth results. This is usually attributed to uterine malposition. (2) The fetus does not die, but is expelled prematurely. (3) The child may (a) present obvious evidences at birth or within a few weeks, or, (b) appear healthy for several years and then develop some syphilitic manifestation as interstitial keratitis, or a bone lesion. (4) Again, a healthy child is born to syphilitic parents whose disease is in a latent condition. (5) The child may exhibit certain stigmata, the result of protoplasmic disturbances, even when no infection occurs. The common dystrophies are the high, narrow palate, hare lip, scaphoid scapulæ, short arms, hypoplastic teeth, etc. (6) The possibility of hereditary syphilis should be suspected in individuals whose chief characteristic is a constitutional inferiority.

LECTURES ON THE EARLY DIAGNOSIS AND TREATMENT OF SYPHILIS.—Jas. H. Sequeira. *British Medical Journal*, January 6, 1917.

Syphilis, as Hutchinson taught, is a great imitator. Always have syphilis in mind, particularly when you see what looks like a common variety of eruptions with usual distribution, and where there is an eruption of several types coexisting. Do not make a diagnosis on the rash alone; look for confirmatory signs in the glands and mucous membranes. Do not pay too much attention to the history, and in any doubtful case take a specimen of blood for the Wassermann test. In cases of which the writer was clinically certain of syphilis, the following results were obtained. Primary syphilis, Wassermann positive in 90 per cent; secondary syphilis, Wassermann positive in

99 per cent; tertiary syphilis, 95 per cent; and congenital syphilis, 100 per cent.

**SURFACE TENSION AND THE WASSERMANN REACTION.**—Vincent B. Nesfield, Major, Indian Medical Service. *Lancet*, London, 1917, vol. xcii, p. 18.

Surface tension is the all important factor in the Wassermann reaction. Alcohol, bile, carbolic acid, and solutions of cholesterin, which act as antigens in the Wassermann test, all have very low surface tension and greatly reduce the surface tension of serum. It is difficult to distinguish a syphilitic antigen from a substance which lowers surface tension. A simple instrument for the measurement of surface tension is described.

**THE HECHT-WEINBERG-GRADWOHL TEST IN THE DIAGNOSIS OF SYPHILIS.**—R. B. H. Gradwohl, St. Louis. *Journal of the American Medical Association*, 1917, vol. lxxviii, p. 514.

The group of cases in which the amount of natural amboceptor in human serum seems to play a definite role in making a Wassermann appear negative and a Hecht-Weinberg-Gradwohl positive, comprises: 1. Cases of ocular syphilis. 2. Cases of visceral syphilis, particularly of the liver and heart. 3. Cases of syphilis that have received intensive but inadequate treatment. 4. Provocative cases in which one seeks to revive a Wassermann in suspected cases. 5. Cases of monosymptomatic tertiaries. It is the author's belief that this test is far superior in every respect to the Wassermann in point of delicacy of control of treatment. Another observation is that when the Hecht-Weinberg-Gradwohl becomes negative as a result of the intensive treatment that is needed to bring this about, it seldom lapses back to positiveness. This test has been a far better check of the Wassermann than the use of any of the controls now in vogue, particularly of the so-called border line Wassermann reactions.

**A CONSIDERATION OF THE SEROBIOLOGICAL REACTION AFTER FIVE YEARS OF OBSERVATION.**—Chas. R. Ball, St. Paul. *Journal of the American Medical Association*, 1917, vol. lxxvii, p. 262.

These reactions should be regarded in the same manner as the symptoms in a clinical picture. They furnish only a part of the information which must be carefully weighed in connection with all the other factors obtained. Often when other symptoms fail they are found to be present, and give the clue to the proper diagnosis. On the other hand, it must not be forgotten that the reverse is sometimes true and they are absent, and then the other symptoms must be depended upon for the diagnosis. In atypical cases, hard and fast rules can not be formulated for these reductions any more than for other symptoms.

A spinal fluid examination should be made in all cases in which symptoms are present, which are referable to the nervous system, unless the etiology of these symptoms is definitely known. In the absence of other symptoms, its findings form the best criteria in deciding when it is safe to stop treatment. In the so-called cases of parasyphilis the last statement does not apply because of the impossibility with the present methods of therapy of obtaining a normal spinal fluid. In nervous syphilis, without other symptoms, a normal spinal fluid means a good prognosis and a recovery; a pathologic one, a latency which at any time may become active.

A SIMPLIFIED COMPLEMENT FIXATION TEST.—Norman E. Williamson, Stockton, Calif. *The Journal of Laboratory and Clinical Medicine*, 1917, vol. ii, p. 202.

Williamson has modified Noguchi's complement fixation test in the following manner: Capillary pipettes are drawn out of small glass tubing. With a light touch of a file a mark is made at the point which 0.06 c.c. of mercury reaches from the end of the capillary tubing. The entire length of the pipette is 12 cm. Blood is drawn from the ear to the mark. This will contain approximately 0.02 c.c. of the serum for each tube of the test as used in the Noguchi test, in addition to cells. Place the small tubes in the rack used for the complement fixation, and add to the front tube 1.94 c.c. of citrated salt solution. The salt solution is the usual 0.9 per cent. The citrate is added in the proportion of 4 parts to 10,000. It is convenient to keep on hand salt solution containing 1 per cent citrate. Four c.c. of this and 96 c.c. of salt solution will make the right proportion for the tubes. This will prevent the clotting of the 0.06 c.c. of blood used, and does not in any way interfere with the reaction. If salt solution alone be used, the slight clot which forms detracts from the accuracy of the test. 0.06 c.c. of blood is put in the front tube and immediately shaken. The blood is taken out of the pipette using the mouth piece of a blood counting pipette. One c.c. is taken from the front tube for the control tube. The pipette is then washed with salt solution, water, alcohol, ether, and dried in the flame of a Bunsen burner. It is now ready for the next patient. Blood is taken from known positive and negative cases for control. Remove and add 3 units of antihumanamboceptor in 1 c.c. of salt solution. A unit of amboceptor has the same meaning as usual; i. e., the quantity which will hemolyze 1 c.c. of 1 per cent suspension of washed human red cells in one hour with 1 unit of complement. Place in water bath at 37° C. for one hour. Compare each front tube with its corresponding back tube. Complete inhibition of hemolysis in the front tube with an average amount in the back tube would be ++. Less than this but more than fifty per cent inhibition would be +. More accurate readings can be made with a colorimeter, using a standard in the wedge and comparing each tube

with the standard. Tubes must either be allowed to settle after incubation or they can be at once centrifugated and read. The amount of red cells used in this test is about equal to 1 c.c. of three per cent suspension or three times that used in the Noguchi test. This is not a disadvantage, as no more will be hemolyzed than the unfixed complement can manage. The hemolysin is always the same, as none is added with the patient's serum. This might occur if serum and cells came from individuals of different groups, unless cells belong to group 4 of Moss, as was mentioned in a former contribution. The advantage in his technic claimed by Williamson is that the blood taking is very simple and relieves the patient of much discomfort. No time is lost in getting clear serum. There is no wasting of blood except for standardization of reagents. The test can be completed in two hours from the time the blood is taken.

A STANDARD METHOD FOR MAKING UNIFORM COLLOIDAL GOLD SOLUTION.

—William K. Trimble, Kansas City, Mo. *The Journal of Laboratory and Clinical Medicine*, 1916, vol. ii, p. 199.

Trimble offers the following technic for the preparation of a standard colloidal gold solution: Distill 500 c.c. of water into an especially cleaned Erlenmeyer flask and place on an iron tripod. Interpose between the flame and the flask a disc of copper about the thickness of a heavy blotting paper. The object of the copper disc is to permit a more uniform heating of the water and at the same time prevent overheating the solution at points in the bottom of the flask. Insert a clean thermometer into the water and when the temperature has reached 65° C. add at once 5 c.c. of the 2 per cent potassium solution. Stir, and when the solution has reached 75° C., immediately add 5 c.c. of the 1 per cent gold chloride solution. Stir, and bring the temperature of the solution to 90° C. Remove the flame and begin adding the 1 per cent formaldehyde solution, quite a few drops at a time, and with constant stirring. It is important not to be hasty in adding the formaldehyde solution. When 3 to 5 c.c. have been added, allow considerable time before more is used, and then only a few drops at a time. In a short while a perceptible change in the color of the solution will be seen, when no more of the formaldehyde should be added. Let the flask remain on the hot copper disc until the solution changes to a bright, clear, deep red color, when the flask is removed and allowed to cool. The color deepens slightly on cooling. It is not necessary to reheat during or after the addition of the formaldehyde solution, so long as the whole remains at 90° C.

THE PRESERVATION OF ERYTHROCYTES FOR THE WASSERMANN REACTION.

—Stanley P. Reimann, Cleveland. *Journal of Laboratory and Clinical Medicine*, 1916, vol. ii, p. 200.

Reimann reports on the preservation of erythrocytes for the Wassermann reaction, using the Rous and Turner method, and a method

employing formaldehyde solution. The technic of the latter is as follows: Sheep's blood is run directly into formalin solution in the proportion of 0.5 c.c. of 40 per cent formaldehyde solution to 400 c.c. of blood. Defibrination is accomplished by shaking with glass beads. The mixture is not disturbed until ready for use, when the cells are washed three times with 0.85 per cent saline solution in the usual way. Under ordinary laboratory conditions sheep erythrocytes for use in the Wassermann reaction can be preserved satisfactorily from 3 to 4 weeks by the formation method, and for from 21 to 25 days by the Rous and Turner method. The readings obtained with fresh cells only, insofar as some sera produce slightly different results when used with cells from the same specimen of sheep blood.

REPORT OF THE COMMITTEE ON UNIFORMITY IN THE WASSERMANN REACTION.—Southern Medical Journal, 1917, vol. x, p. 110.

The following committee was appointed by the President of the Southern Medical Association to investigate the Wassermann reaction in regard to the establishment of a uniform technic: Dr. Albert Keidel, Dr. Loyd Thompson, Dr. J. A. Lanford, Dr. H. L. McNeil, Dr. William Litterer, and Dr. Chas. Watterston. This committee reported that the variation in results obtained by different investigators was attributable to four factors. First, wide variation in the technic and the reagents employed. Second, failure to standardize all reagents before each test. Third, lack of controls of patient's serum and the antigen in each and every test. Fourth, irregularities in the character and preparation of the antigens employed. A standard technic has not been adopted by this committee and will be the subject of a further report.

A STUDY OF THE CEREBROSPINAL FLUID IN FIFTY CASES OF CEREBROSPINAL SYPHILIS.—Chas. Clyde Sutter, Rochester. New York State Journal of Medicine, 1917, vol. xvii, p. 23.

In this analysis fifty cases of syphilis of the central nervous system have been observed. There were ten cases of cerebrospinal syphilis, eleven cases of tabes dorsalis, twenty cases of general paresis and nine cases of tabo-paresis. The signs and symptoms of cerebrospinal syphilis are quite manifold and varied. In the cerebrospinal fluid we find a more constant picture. Almost every case shows a strong globulin reaction, a positive gold chlorid reaction and a positive Wassermann reaction. In the eleven cases of tabes dorsalis most of the examinations were made after the patient had been given considerable treatment. This alters the findings somewhat. The globulin reaction was present in seven cases, weakly positive in two, and negative in two out of the eleven cases. The cell count was increased in eight, normal in one, and border line in two cases. The highest count was fifty-five. The Lange gold chlorid reaction in the series of eleven

cases did not show any characterisite curve. The Wassermann reaction was positive in the serum in five cases and in the blood in seven cases. In one case it was negative in the serum and positive in the blood. The strongest and most characteristic reactions were seen in the twenty cases of paresis. All cases showed well marked color changes in the Lange colloidal gold chlorid reaction. The typical paresis curve was seen in all the tests. The highest cell count was fifty. It was normal in two cases and only a slight increase in another. The globulin was positive in sixteen cases, weak in two, and negative in two cases. The Wassermann reaction was positive in every case except two. In all cases of tabo-paresis all the tests were positive; the cell count varied from two to seventy; the globulin was strongly positive in all but one case. In the light of our present knowledge, lumbar puncture with cerebrospinal fluid examinations is demanded in all cases of syphilis.

WASSERMANN PARADOXUS.—D. M. Kaplan, New York. *New York Medical Journal*, 1917, vol. cv., p. 444.

In using two antigens one finds that the cholesterinized extract is usually the one that gives a more complete inhibition than the crude alcoholic nonreinforced product. It is by no means a rare occurrence to have complete hemolysis with the latter and equally strong inhibition with the former. Upon a closer analysis from the clinical point of view a very interesting situation disclosed itself. This paradox Wassermann invariably came from patients who displayed one or more manifestations of motor unrest, such as spasms, ties, tetanoid movements, fainting spells, and convulsions. Many presented that type of epilepsy that still parades under the designation of "idiopathic." All of them showed no signs of lues in their physical analysis or in their history. A few cases were given the benefit of the doubt, but neither mercury or salvarsan nor the combined treatment showed any improvement in these cases. The Wassermann paradoxus should always be guarded against, as it may cause trouble when only nonreinforced extracts are used. The situation has nothing to do with lues, but rather with a neural state that permits a deviation of the complement in the absence of cholesterolin.

EARLY DIAGNOSIS OF TABES DORSALIS.—Walter F. Schaller, San Francisco. *Journal of the American Medical Association*, 1917, vol. lxxvii, p. 190.

Every case of syphilitic posterior leptomeningitis and consequent multiple symmetrical radiculitis is a case of potential tabes. This meningeal reaction is evidenced in the cerebrospinal fluid by an increased cell count and increased globulin content; and probably also by a positive Wassermann reaction indicating that this reaction is syphilitic in nature. During certain stages in the evolution of tabes,



probably of repair, these reactions may be negative. It is therefore necessary to make repeated puncture in doubtful cases. The Achilles tendon reflexes are lost as a rule before the patellar tendon reflexes; this phenomenon was observed in ten cases of primary optic atrophy from a total of thirteen cases. Anisocoria and pupils of definitely irregular contour are found frequently in early tabes. These pupillary signs, even in the absence of the Argyll-Robertson pupil, are highly characteristic of early tabes, provided there is no local assignable cause. The symptom of diminished hearing is frequently encountered in early tabes. Cardiovascular disease, especially aortic diseases, and general glandular enlargement are frequently found in tabes, thus giving evidence of syphilitic processes elsewhere in the body. In a patient with a history of other evidence of syphilis presenting characteristic sensibility disturbances of the radicular type with a tendency to symmetry, one should suspect a potential or early tabes. If, associated with the foregoing, we have a positive reaction in the cerebrospinal fluid indicating a chronic syphilitic meningitis, together with such pupillary phenomena as anisocoria, pupillary irregularity or sluggish reaction to light, the diagnosis of early tabes is most probable. Added to the foregoing symptoms, the loss of the Achilles tendon reflex establishes the diagnosis of early tabes even in the absence of those signs which we usually associate with tabes: Romberg, marked sensibility loss, absent patellar reflexes, and Argyll-Robertson pupils.

MERCURIALIZED SERUMS.—Lloyd Thompson, Hot Springs, Arkansas.  
New York Medical Journal, 1917, vol. cv, p. 123.

In order to overcome the phlebitis and periphlebitis which sometimes follow the ordinary intravenous injection of mercury, Thompson prepares a mercurialized serum as follows: From 40 to 50 c.c. of blood are collected by venipuncture and placed in a large test tube which has been boiled in salt solution. After separation the serum is poured off and thoroughly centrifugated. A watery solution of mercuric chloride is prepared so that each cubic centimeter contains 22 mg. ( $\frac{1}{3}$  grain) of the salt. The serum is now measured and divided into two parts, one-third of the amount placed in one tube and the remainder in another. The mercury solution is added to the first part in the proportion of 1 c.c. to each 2 c.c. of the serum. A heavy precipitate of albuminate of mercury appears, which is completely dissolved on the addition of the remainder of the serum. It will be seen that the mixture will contain 22 mg. ( $\frac{1}{3}$  grain) of mercuric chloride in each 7 c.c. At first great difficulty was encountered in keeping the albuminate of mercury in solution for any length of time, and it was necessary to prepare the solution fresh before each injection, but later it was discovered that if the mixture is heated in the water bath for one-half hour at 35° C. it will remain in solution indefinitely. Ascitic and hydrocele fluids may also be used, but the mercurialized serum

prepared from horse serum, which has been placed upon the market, is not recommended, owing to the danger of anaphylaxis.

MERCURIALIZED SERUM.—F. E. Stewart, Philadelphia. *New York Medical Journal*, 1917, vol. cv, p. 121.

Corrosive sublimate becomes noncorrosive and nonirritating when dissolved in normal serum. The compounds thus formed are just as toxic and probably therapeutically as efficacious as mercuric bichloride itself. When prepared from heterologous serums, mercurialized serums must be regarded as heterologous serum preparations, requiring conformity to the same rules in their administration as applied to other heterologous serums, such as diphtheria antitoxin and antibacterial serums. Mercury in the form of mercurialized serums is an ideal form for administering mercury subcutaneously, intravenously, and intraspinally. Subcutaneous or intramuscular administration is the method of choice. Intravenous or intraspinal administration should be the method of resort only when especially indicated.

MERCURIALIZED SERUM AND BICHLORIDE OF MERCURY.—Paul S. Pittenger, Philadelphia. *New York Medical Journal*, 1917, vol. cv, p. 161.

Mercurialized serum, whether injected intramuscularly, intravenously, or intraspinally, is equally toxic as corresponding amounts of plain bichloride of mercury. The addition of an excess of serum to bichloride of mercury does not reduce its toxic properties but merely deprives it of the property of destroying tissue by precipitating and then dissolving the albumin of the tissue, without changing its toxicity or therapeutic efficiency. Intramuscular or subcutaneous injections of mercurialized serum are practically painless and are not followed by sensitiveness, pain or sloughing, which usually accompanies injections of the plain bichloride. Intravenous injections of mercurialized serum are not followed by pain or sensitiveness at the site of injection. Overdoses of mercurialized serum when administered intravenously produce the same untoward effects, such as blood in the stools, vomiting, retching, markedly increased and troubled respiration, etc., as plain bichloride of mercury, and care should be used, therefore, not to produce toxic effects by overdoses or administration at too frequent intervals. Mercurialized serum in proper doses may be safely injected into the spinal canal. In systemic syphilis very favorable results can be obtained by intramuscular or subcutaneous injections of mercurialized serum. Intramuscular or subcutaneous administration of mercurialized serum is to be preferred in the treatment of systemic syphilis, except in patients where quick results are imperative, in which case the serum may be administered intravenously.

THE COMBINATION OF SULPHUR AND MERCURY IN THE TREATMENT OF SYPHILIS.—M. Leoper, A. Bergeron, and K. Vahram. *Le Progres Medical*, January, 1917.

These observations are based on two thousand injections, of which five hundred were intravenous and fifteen hundred intramuscular. The ampoules which were used contained to each cubic centimeter  $\frac{1}{2}$  millimeter of sulphur, and  $\frac{2}{3}$  millimeter of mercury, and  $\frac{1}{6}$  millimeter of sulphur, and  $\frac{4}{6}$  millimeter of mercury; 1 or 2 c.c. were used at a dose. The first effect upon the blood was a polynuclear leucocytosis for which was progressively substituted a mononuclear leucocytosis with a slight eosinophilia and slight myelocytosis. One hundred and sixty-six cases of syphilis were treated. The first fourteen cases were primary; thirty-two secondary; one hundred and twenty tertiary, and eight hereditary syphilis. The localization was cutaneous, 34 cases; mucous membrane, 20; glands, 3; osseous or osteoarticular, 41; pulmonary and laryngeal, 6; hepatic, 3; gastric, 4; ocular, 9; renal, 12; and arterial, 13. In a general way the results were very good in 80 per cent of cases; fairly good in 10 per cent and mediocre or negative in 6 per cent. In some cases the results are very rapidly attained. In one per cent of the cases three injections sufficed; in 2 per cent four; in 3 per cent five; in 6 per cent seven; in 50 per cent eight; 50 per cent of cases were cured after ten injections; 10 per cent required fifteen or twenty injections; and in only three per cent did the number exceed thirty or forty. The combination of sulphur and mercury appears to render genuine service in manifestations of syphilis.

A NEW MERCURIAL PREPARATION IN THE TREATMENT OF SYPHILIS.—Maurice F. Lautman, Hot Springs, Arkansas. *Medical Record*, 1917, vol. xci, p. 60.

An emulsion of 10 per cent mercury benzoate and 2 per cent quinine and urea hydrochloride in white petrolatum makes an excellent preparation for intramuscular injections in syphilis. It is no more painful than any of the other preparations in use, and permits of giving three grains of the salt each week. In twenty-five unselected and previously untreated cases the blood Wassermann was changed from a four plus to a negative in an average of eight weeks. The influence on the existing lesions was very favorable. This communication is not intended to convey the impression that a negative Wassermann means that the syphilitic process has been cured or arrested, but the favorable effect on the Wassermann reaction would seem to indicate that the process had been temporarily controlled.

SYMPTOMS FOLLOWING INJECTION OF NEOSALVARSAN.—A. M. Moody, Chicago. *Journal of the American Medical Association*, 1916, vol. lxvii, p. 1757.

In several cases chills with headache, nausea, diarrhea, and in some instances, vomiting, have followed a single injection of neosalvar-

san. The onset of these symptoms may be immediate or delayed from one to twelve hours or more. The author has records of only one death following intravenous injection of salvarsan. The patient, a woman, was injected Thursday at 3 p. m., and received 0.9 gm. of neosalvarsan. The patient was in poor condition when the injection was made. She later developed headache, chills, and backache. Friday night she went into coma and died at 10 a. m. Sunday with what the physician described as symptoms of arsenical poisoning. These findings were not confirmed by postmortem examination.

TOXICITY OF THE PRESENT SUPPLY OF SALVARSAN AND NEOSALVARSAN.—Oliver S. Ormsby and James H. Mitchell, Chicago. *Journal of the American Medical Association*, 1916, vol. lxvii, p. 1756.

Reaction following the injection of the present neosalvarsan differs from that of salvarsan in that there is a marked tendency to nausea and vomiting. The striking increase in the number of severe reactions following the use of salvarsan as now supplied, indicates a high degree of toxicity. That salvarsan too is more toxic than formerly, is indicated by the number of cases in which immediate vomiting occurs.

TOXICITY OF SALVARSAN.—John D. Ellis, Chicago. *Journal of the American Medical Association*, 1916, vol. lxvii, p. 1757.

In a great majority of cases in which Ellis has used the salvarsan purchased during the last three months, he has noticed some toxic symptoms. Fully half of these patients have suffered from repeated vomiting after an intravenous injection. Intravenous injections of salvarsan purchased prior to that time rarely resulted in vomiting or in toxic symptoms.

A COMPARATIVE STUDY OF SALVARSAN AND NEOSALVARSAN IN THE TREATMENT OF SYPHILIS.—Wm. B. Trimble and John J. Rothwell, New York. *Journal of the American Medical Association*, 1916, vol. lxvii, p. 1984.

The report is based on the treatment of one hundred and ten patients to whom three hundred and ninety-seven injections were given, and on whom three hundred and thirty-seven Wassermann tests were performed. A course of four injections of either salvarsan or neosalvarsan is inadequate treatment. A series of injections of salvarsan, either old or new, not followed by mercurial treatment produces extremely few negative serum results. From four to six salvarsan or neosalvarsan injections, even when followed by mercury, produces only a comparatively small percentage of negative serum results. According to this study, neosalvarsan is superior to salvarsan, being much easier of administration, less likely to cause severe reaction, and producing a greater percentage of negative results.

THE ADMINISTRATION OF ARSENOBENZOL BY MOUTH.—Jay F. Schamberg, John A. Kolmer and George W. Raiziss, Philadelphia. *Journal of the American Medical Association*, 1916, vol. lxxvii, p. 1919.

In a general way it may be stated that about one-ninth or one-tenth of a dose required in solution by mouth, produces the equivalent effect intravenously. Arsenobenzol in capsules exerts, however, about forty to fifty per cent of the trypanocidal effect produced by neosalvarsan intravenously. Clinically, it has been found that the drug may be given in doses of 30 mg. ( $\frac{1}{2}$  gr.) three times a day for many weeks without producing disturbing symptoms, except mild digestive distress, and this is only in a relatively small proportion of cases. Administered by mouth, arsenobenzol is capable of producing a curative influence on the lesions of syphilis. The effect, however, is much less vigorous than when the drug is administered intravenously. We do not advise the use of arsenobenzol by mouth as a routine, inasmuch as there are more efficient avenues of administration. Its use is to be reserved for patients who, for some reason, can not take the drug by intravenous infusion or by intramuscular injection.

DEATH AFTER SALVARSAN.—Maneck D. Wadia, Sumerpur, India. *British Medical Journal*, January 6, 1917.

The case reported was in a male aged twenty-three years who had a chancre about six weeks before which healed under treatment and now presented a typical secondary rash with mucous patches in the mouth, and general adenitis. A physical examination was negative. On May 23rd he was given intravenously 0.5 of a gram of salvarsan at 10 A. M. He had a good deal of vomiting and diarrhea, and rapid, feeble, but regular pulse, during the day and was rather restless during the night. On May 27th he was all right, but weak. On the morning of the 29th he was typically jaundiced and the urine contained traces of bile and albumin. On May 30th he suffered from hiccough. On June 1st the jaundice was deeper and the urine showed traces of bile and albumin but no casts or crystals of leucin or tyrosin. On June 3rd, his condition was worse, the temperature 99, pulse 70, and feeble. Jaundice was the same and the liver was still enlarged and tender. The blood examination was negative. The rash had faded a little, but the ulcers in the mouth and on the lips were worse. On June 5th, at 5 P. M. he collapsed and died. A post-mortem examination was not allowed. The interest in the case here recorded lies in the long period between the administration of the salvarsan and the manifestation of toxemia. The symptoms would suggest acute yellow atrophy or phosphorous poisoning, but both are negatived by the fact of there being enlargement of the liver throughout, and also as to the former by the absence of leucin and tyrosin

in the urine. There must have been a storage of arsenic in the liver giving rise, in all probability, to acute degenerative changes in the cells.

THE TREATMENT OF SYPHILIS WITH ARSENICAL PREPARATIONS.—E. H. Martin, Hot Springs, Arkansas. *Southern Medical Journal*, 1917, vol. x, p. 201.

In all ordinary cases old salvarsan is the only drug which should be used. It will cure all cases of syphilis which are curable, and give the best results in the treatment of such cases as are not curable. If a patient, after sufficient salvarsan treatment to abolish the anti-toxin reaction and render the Wassermann negative, returns in a few months, or even in a year or two, with a history of suspicious intercourse followed in three or four weeks by a typical hard chancre, he has had a reinfection. That such infection occurs only after the thorough use of salvarsan, proves that salvarsan, and salvarsan only, will in some cases cure syphilis. No other drug will do this. For this reason, the author has afflicted no patient with mercury during the past five years, except at his own request, or at the request of his home physician. It is his opinion that it is not only unnecessary to use mercury in the treatment of syphilis, but in most cases, unforgivable. When we give a full dose of salvarsan we should expect to kill only the mature and accessible spirochetes. The next dose should be given well within the accepted period of incubation. Seven day intervals work satisfactorily. A primary case may show a softening of the chancre site after the first dose of salvarsan and a dose or two more may eradicate the disease. During the secondary stage of syphilis it is most easily eradicated. At this stage two doses of salvarsan will frequently sterilize the host of spirochetes, but usually it is safer to give three or four doses. When persistence of the anti-toxin reaction after each dose occurs, one may consider the case an early tertiary. Many of the symptoms of tabes yield to treatment, and in most cases, the cause of the disease may be arrested by persistent intravenous dosing with salvarsan. The writer's experience with the intraspinal method of treatment has been limited and unsatisfactory, with the intracranial method nil, but a careful survey of results reported by the enthusiasts on this method does not show any advantage over the results he has obtained from persistent intravenous treatment.

MODERN DIAGNOSIS AND RESULTS CLINICALLY, SEROLOGICALLY, AND SOCIOLOGICALLY OF SYPHILIS.—Benjamin A. Thomas, Philadelphia. *Journal of the Pennsylvania State Medical Association*, 1917, vol. xx, p. 254.

Based on a study of five hundred and ten cases of syphilis, the author concludes that the treatment of syphilis, notwithstanding the promise of salvarsan and its substitutes, judged from the excellent

serological results extending in many instances over several years, remains empirical. The ultimate proof of cure does not rest necessarily upon continuous Wassermann reactions for one, two, three, four, five, ten, twenty, or even forty years, but rather upon complete freedom of symptoms for a generation or more. The Wassermann reaction furnishes the best control of treatment, and is the most reliable index of cure subsequent to proper treatment. The sheet anchor in the treatment of syphilis is no longer mercury, but salvarsan, neosalvarsan, or one of their substitutes. Secondary syphilis seems to do just as well without as with mercury, provided enough salvarsan or neosalvarsan be given to produce a negative Wassermann. The serological results in tertiary syphilis treated intensively with salvarsan and its substitutes are not so brilliant as those of the secondary period. The best substitute for salvarsan and neosalvarsan is the Polyclinic preparation of arsenobenzol, which although apparently not so effective in eradicating the Wassermann, is essentially devoid of any serious toxicity, even less so than neosalvarsan. The arylarsionate "soamin" and sodium cocodylate, both clinically and serologically, have no place in the effective treatment of syphilis. Sociologically, in view of the fact that only ten per cent of our hospital syphilitics return for treatment until discharged cured, a problem is presented which urgently demands the cooperation of our civil authorities and health boards for the necessary control and treatment of this disease, not, however, to be realized until all hospitals receiving state aid are compelled to maintain evening dispensaries with paid attendants for the proper treatment and admission when necessary, of venereal patients.

THE STUDY OF SODIUM COCODYLATE IN THE TREATMENT OF SYPHILIS.  
—H. N. Cole, Cleveland. *Journal of the American Medical Association*, 1916, vol. lxxvii, p. 2012.

At the utmost, sodium cocodylate has, perhaps, a slight action on the papular and nodular syphilides, but in no case is it to be compared with even mercury and potassium iodide alone. It is probably to be explained entirely from the tonic action of the arsenic on the skin. In cases of syphilis with mucous patches, it is worse than useless. In one of the author's cases there was a drop in the spinal fluid cell count from sixty-five to twenty-five, but the Wassermann and Noguchi tests remained positive, and two other cases with cerebrospinal involvement showed practically no change. Five-tenths of a gram was used every three days and routine urine examinations in two cases out of a total of ten studied, showed red cells and albumin, the one after four and the other after six injections. The routine positive blood Wassermann in all ten cases was in no instance changed to negative.

NOTES ON THE TEACHING AND TREATMENT OF SYPHILIS.—H. G. Irvine, Minneapolis. *Journal of the American Medical Association*, 1916, vol. lxvii, p. 1987.

The majority of schools have competent men in charge of this work, but results, in many cases, are not obtained on account of the school not furnishing sufficient assistants and adequate equipment. The prevalence of the late manifestations of syphilis is obvious proof that the profession has not treated syphilis adequately; there is no excuse for the continuance of these methods.

SHALL WE TREAT THE PARETIC?—C. Eugene Higgs and E. M. Hammes, St. Paul. *Journal of the American Medical Association*, 1917, vol. lxviii, p. 194.

The authors believe that by intraspinal medication, remissions are greatly increased in frequency; that in early paresis, marked improvement may occur with a possible arrest of symptoms. Of twenty-one patients treated with salvarsanized serum intraspinally, according to Swift-Ellis methods, with and without mercury intramuscularly, ten showed a decided improvement. Both clinically and biologically it has been demonstrated that treatment is a material benefit to the paretic. Before the salvarsan era, the number of remissions varied from 4 to 20 per cent. Since its use and the employment of modern forms of therapy, they have been greatly increased in frequency. Treatment to be effective in paresis, must be given in its earliest stage; in cases of long standing it is useless; cell destruction can not be replaced. Also, to be effective, it must be persistent. It may be a matter of months before the activity of the infection can be influenced.

A NEW METHOD FOR INTRASPINOUS TREATMENT OF NEURAL SYPHILIS WITH MERCURY.—Maurice F. Lautman, Hot Springs, Arkansas. *New York Medical Journal*, 1917, vol. civ, p. 1281.

To saturate the patient with mercury, daily inunctions are given of one-fourth of an ounce of fifty per cent mercurial ointment, supplemented by tri-weekly intramuscular injections of any one of the mercurial salts. These procedures are continued until the first evidences of pyalism appear, when 30 c.c. of blood are removed by venipuncture. The rest of the technic is similar to that used in the Swift-Ellis method; the blood is allowed to clot and the 10 or 15 c.c. of serum obtained is pipetted off and centrifugated to remove all of the blood cells. One c.c. of a solution of one grain of mercury benzoate in 25 c.c. normal saline is placed in a clean test tube and boiled. If on cooling this solution becomes turbid, it should be discarded and another cubic centimeter of the solution boiled up in the same tube. If this remains clear on cooling, the clear serum is added and the



preparation is mixed well. It is then heated at 56° C. for half an hour and administered by gravity, at body temperature. The method of administering the serum is essentially the same as that recommended by Swift and Ellis. The method was used in eighteen cases, though the present report contains the records of the first ten cases which completed the course of injections. The cases were unselected and embraced almost all the forms in which neural syphilis manifests itself. In all of the cases, after from three to six injections, the spinal fluid was rendered normal. The extent of the clinical improvement and the restoration to economic efficiency seem to depend upon the extent of degeneration at the time the treatment was instituted. In no case was there further deterioration during or after the treatment. Neither was there any case in which the spinal serology could not be influenced. The results in the cases treated were uniformly favorable, and there is no hesitation in recommending the method for the treatment of syphilis of the central nervous system.

TREATMENT OF CEREBROSPINAL SYPHILIS WITH REPORT OF CASES.—  
L. W. Grove, Tuscaloosa, Ala. *American Journal of Insanity*,  
October, 1916.

It is too early in the modern treatment of cerebrospinal syphilis to draw definite conclusions, but evidence shown warrants the efforts in early cases. There is little to be hoped from treatment in advanced cases, hence the crying need of an early diagnosis. Negative history and blood might prove misleading, hence the necessity of serum reaction on spinal fluid. There is strong evidence to show that injurious effects might come from too large a dose of antisiphilitic agents intradurally. The thorough saturation of the system with antisiphilitic agents is the end hoped for, hence all methods of treatment should be relied upon used conjointly.

MERCURIAL MEDICATION WITH SPINAL DRAINAGE.—L. B. Pilsbury,  
Lincoln, Nebr. *Journal of the American Medical Association*,  
1917, vol. lxviii, p. 267.

On theoretical grounds it does not seem that the removal of from 20 to 40 c.c. of fluid once every week or two should have more than a very transient effect in reducing pressure, and it seems probable that spontaneous variations in pressure may occur from time to time, though doubtless in less degree. The fluid is probably rapidly replaced after withdrawal, and it is possible, of course, that the very rapidity might have a tendency to carry over foreign substances which happen to be circulating in the blood at that particular time. Ten cases of paresis, taboparesis and cerebrospinal syphilis were so treated, that is, the patients were given mercurial inunctions 1 dram six days in the week, and were punctured every two weeks with few variations. In most cases the inunctions were continuous. They

were not selected patients, but would represent about the usual hospital run, and some would be a severe test for any form of treatment. The amount of fluid withdrawn varied from 20 to 35 c.c., the Wassermann was performed with 1 c.c. fluid and the cells were counted in a Thoma-Zeiss chamber with the higher power. On the whole, the results are not striking, and similar effects might reasonably be expected without any spinal drainage. One of the patients is decidedly better and several are slightly so, but the one who improved the most had an alcoholic as well as a syphilitic factor. None have been treated in this fashion for more than four months and none for less than ten weeks, and this is perhaps not time enough for a maximum amount of benefit.

**INTRASPINAL TREATMENT OF NEUROSYPHILIS WITH STANDARDIZED SERUM.**—Willard C. Stoner, Cleveland. *Journal of the American Medical Association*, 1917, vol. lxviii, p. 610.

The value of intraspinal therapy as an adjunct to the treatment of neurosyphilis has been established. The technic used is that devised by Ogilvie, which is a modification of the Swift-Ellis method. The number of treatments given was 252. Of the 72 patients, 12 were given only one injection, and hence are not considered in determining results. The average number of treatments given a single patient was four. The maximum number was twelve. The seventy-two cases consisted of the following classification: Cerebrospinal syphilis, 6; cerebral, 15; spinal, 6; tabes, 26; paresis, 6; congenital syphilis, 1; syphilitic endarteritis, 2; spinal myelitis, 2; 1 case of psychosis of questionable classification with positive Wassermann on blood serum and negative lumbar puncture findings; cases in which the clinical picture was only suggestive and treatment was provocative, and hence unclassified, 8. The results of treatment are as follows: Lymphocyte count made normal, 40 per cent; Wassermann made negative on cerebrospinal fluid with 0.5 c.c.,  $11\frac{2}{3}$  per cent; globulin content of fluid made negative, 20 per cent; negative lumbar puncture made positive by treatment and hence provocative,  $13\frac{1}{3}$  per cent; made normal in lumbar puncture findings, 10 per cent; improved but not made normal in one or more findings,  $38\frac{2}{3}$  per cent; alternate intravenous or simultaneous treatment with either salvarsan or mercury, 45 per cent; no intravenous treatment with intraspinal treatment, but intensive intravenous and mercurial treatment previously, 5 per cent; both previous intravenous treatment and alternate in conjunction with intraspinal,  $38\frac{1}{3}$  per cent; only intraspinal treatment,  $11\frac{2}{3}$  per cent; completely relieved of all annoying symptoms and apparently made well, 20 per cent; improved in one or more symptoms, but not completely relieved,  $66\frac{2}{3}$  per cent; improved and afterwards relapsed,  $\frac{1}{3}\%$ ; no improvement (two advanced paretics, now dead) 10 per cent.

THE TREATMENT OF SYPHILIS OF THE CENTRAL NERVOUS SYSTEM WITH INTRASPINAL INJECTIONS OF MERCURIALIZED SERUM.—Julian Mast Wolfsohn, San Francisco. *American Journal of the Medical Sciences*, 1917, vol. cliii, p. 265.

The technic used was that after one week of full doses of mercury, 40 c.c. of blood were collected, centrifuged, and after standing in the refrigerator from eighteen to twenty-four hours, it was again centrifuged, and 18 to 20 c.c. of serum were pipetted off. One c.c. of the solution of mercuric chloride distilled water, which contains 1/50 of a grain of bichloride, was added to the serum, which was then heated at 56° C. for half an hour. This serum was injected by gravity at body temperature. There is no danger in the administration of the serum in this manner. For local treatment it is very efficacious in syphilis of the nervous system, especially in the treatment of tabes, in which lancinating pains are the predominating symptom. Due to its stability, the serum may be used at any time after its preparation. The lack of expensive drugs used in its preparation makes it invaluable at this time. There is no objection to combined salvarsanized and mercurialized treatment. It must not be concluded from the short space of time (eight months) that has elapsed since the beginning of this form of treatment in these cases that relief is going to be permanent. One will have to be cautious about prognosticating a cure until the proper length of time elapses; e. g., at least three years. From the results obtained so far, it certainly has mitigated the symptom of pain.

SALVARSAN AND NEOSALVARSAN IN SYPHILIS.—Oliver S. Ormsby, Chicago. *Journal of the American Medical Association*, 1917, vol. lxviii, p. 949.

Salvarsan and neosalvarsan are the most efficient drugs yet discovered in the treatment of syphilis. Alone they have completely eradicated the infection in early cases before the Wassermann reaction has become positive. The large number of reinfections testify to this fact. Yet even in these cases mercury is recommended as an adjunct. In all other cases, mercury should always be an accompaniment of salvarsan, and in many cases potassium iodide is indicated, especially in the so-called tertiary and latent cases and in those involving the nervous system. The ability of potassium iodide to remove infiltrations, gummata and nodules, together with its marked effect on vascular implications, renders its use imperative. The major number of reactions following the use of salvarsan and neosalvarsan are insignificant. The more serious ones are to be avoided, so far as possible, by an initial small dose to test the tolerance of the patient, by careful attention to details in administrative technic, by recognizing contraindications, and, in the case of early, active syphilis, pre-

ceding the salvarsan treatment with mercury, to prevent neurorecurrences; and finally, by giving sufficient treatment to control the disease. Emphasis must be laid on the latter statement, as much harm may be done by its apparent effect, the degree of relief placing the patient in a position of false security; therefore, sufficient treatment is demanded to prevent recurrences and relapses. Many of the earlier cases, following insufficient treatment, of rapid onset of symptoms which ordinarily come late in the disease, such as nervous involvement and precocious tertiary manifestations, were eradicated by more salvarsan, and now should be entirely avoided by treatment of sufficient intensity and amount to control the disorder. The treatment of syphilis with salvarsan and neosalvarsan has caused an intensive study over the entire world of the question of efficient management of the disease, to such a degree that great lessons have been learned and much good accomplished. Their ultimate value will require many more years to determine. As to a choice between the two drugs, salvarsan and neosalvarsan, the extensive use of both proclaims their efficiency so that individual circumstances with the physician and patient must decide which, under the circumstances, is to be selected. The apparent preponderance of opinion that salvarsan is more efficient is offset to a degree by the difficulties of its administration and the more frequent reactions following its use. The problem of reducing toxicity to a minimum rests with the producers of the drug. Concerning the dangers following the individual injections, many warnings have been given to exercise care after the fourth injection. The warning has not been accompanied by tabulated results showing proof of this contention. On the other hand, the statistics now available show that the major portion of severe reactions, untoward results, and fatalities have followed the first injection, and that with subsequent injections these results were greatly decreased.

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## Original Articles

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### THE TREATMENT OF GENERAL PARESIS

#### A REPORT OF FIFTY-FIVE CASES

BY HANSON S. OGILVIE, M.D., NEW YORK CITY

(Received for publication, June 15, 1917)

THE field of therapeutic possibilities is unquestionably more limited in neurology and psychiatry than in any other departments of medicine. This is in part due to our lack of knowledge regarding the etiologic factors responsible for a large percentage of nervous disorders, in part to the inaccessibility of the affected areas to curative agents, and, in part to the fact that the reparative properties of neural tissue are lower than that of any of the other body tissues so that functions impaired as the result of destructive influences are rarely if ever completely restored.

Research of the past few years, however, has revealed information of the greatest value regarding the etiology, pathology, and therapeutics of a group of diseases now commonly referred to as "syphilis of the central nervous system." Of this group the most destructive is general paresis. While clinically not so common as the other forms of neurologic syphilis, it is by far the most important from a therapeutic point of view. While pursuing a markedly varied clinical course, it has exacted a toll, sooner or later, that has placed it among the first of the list of "incurable" conditions. Generally regarded as one of the most treacherous and dangerous diseases known,

it has, when once established, persistently defied every effort to control it.

The apparent beneficial influence of an intercurrent infection with pyrexia has been noted for a number of years. Perhaps one of the earliest contributions to this phase of the subject was Baillarger,<sup>1</sup> who, in 1849, reported a most remarkable remission in a paretic following a series of furuncles. Many other reports, of a more or less similar character, can be found in the literature. In most instances this type of remission followed some suppurative condition in the body, either acute and severe with very high temperature, or a mild septic condition with a moderate amount of fever extending over a period of weeks or months. In 1870 Nasse reported "recovery" of a case following an attack of smallpox. Fritsch<sup>2</sup> reported a remission following erysipelas. In 1884 C. B. Burr, then Physician to the Eastern Michigan Asylum, at Pontiac, published an article entitled "Amelioration of Paretic Dementia Following Extensive Sloughs."<sup>3</sup> Observations of this kind had led Jacobi, L. Meyer,<sup>4</sup> Sander,<sup>5</sup> Olbeke,<sup>6</sup> and others to attempt to produce inflammatory processes with supuration artificially by rubbing irritating ointments, composed of antimony, cantharides, etc., into the shaved scalp and other parts of the body. In later years Donath's salt infusion,<sup>7</sup> his nucleinate of soda,<sup>8</sup> and von Wagner's tuberculin<sup>9</sup> injections were employed as therapeutic agents. These methods were purely empirical, and while yielding promising results in some instances (particularly Pilez's series in which 26% of remissions were recorded with von Wagner's tuberculin), they did not prove efficacious to a degree that would warrant their recognition as therapeutic measures. In view of these facts it was natural that, with development of progress in the preparation of a curative agent along rational lines, based upon a new and scientifically accurate conception of the pathological process and its etiology, interest in the subject should be renewed and accentuated.

In the five years that have elapsed since Swift and Ellis introduced their intraspinal or subdural method of treatment of syphilitic affections of the central nervous system with salvarsanized serum, a very considerable amount of work has been done in this field in different parts of this country and abroad. A few men have given the serum intracranially, by trephining the skull and penetrating the dura with a needle. More recently Hammond and Sharpe have ad-

vocated, and somewhat extensively employed, the intraventricular method of administration. Their results so far are very encouraging, and the technic employed is much simpler than would naturally at first be assumed.

Theoretically the Swift-Ellis intraspinal method was founded on well recognized scientific principles, both from an anatomic and physiologic point of view, and the originators submitted unquestionable evidence of its practical value in their earliest contributions to the subject. It was met with condemnation in some quarters but so has every new departure from traditional teachings. Some of our most valuable therapeutic measures were long subjected to destructive criticisms before evidence was finally established that gave them their proper places in medicine. The criticisms that have been made of this procedure have, for the most part, come from a comparatively small school that claims to be able to accomplish as much, both clinically and sero-biologically, with the old methods of treatment. It has been pointed out that the actual salvarsan content of a serum that can be given intraspinally without jeopardy to the patient is necessarily so small that its value as a curative agent is questionable. Yet it is possible to administer a much larger quantity in this manner than has ever been found in the cerebrospinal fluid after the most intensive intravenous treatment with the drug. At the same time it seems absurd to reject a curative agent because the necessary active principle is present in a relatively small amount. If this doctrine were followed in the preparation of all therapeutic agents, it is needless to say that many that are now practically indispensable would be rendered worse than useless because of their toxicity. Furthermore, curative agents, drugs and serums alike, are potent in much smaller quantities when given subdurally than when given intravenously. Lewandowsky<sup>10</sup> showed that strychnia was ten times as efficacious when given intraspinally, and that sodium ferrocyanide was potent with one-hundredth the amount required for intravenous administration. A serum containing only a small fraction of a milligram of salvarsan has been shown to possess positive spirocheticidal properties. Young<sup>11</sup> found that the serum and salvarsan formed a colloidal combination, and that a salvarsanized serum could not be dialyzed through a colloidin membrane, although salvarsan alone is dialyzable. This proves that the two substances unite to form a third, the chemobiological and curative properties of which

have further been shown to differ essentially from those of either of the originals.

The method has also been criticized on the grounds that it is a hazardous procedure. This impression, no doubt, resulted from the violent reactions, and in some instances permanent injury to the cord, resulting from the administration of plain neosalvarsan intraspinally, in quite a number of cases. This method was advocated by Ravaut<sup>12</sup> who gave as much as twelve milligrams of the drug in isotonic sodium chloride solution. His original technic was quickly abandoned in this country but several modifications have been suggested and advocated from time to time. While I have never employed the method or any modification of it, from the results I have seen at the hands of others, I have come to regard it as extremely dangerous. Furthermore any method that has for its object the introduction of plain salvarsan or neosalvarsan into the subdural space is, in my opinion, unscientific in principle. Neither one of these drugs is a true spirocheticide *per se*. They serve to perfect a potent spirocheticidal agent only when in combination with blood serum, and (as has been shown by Swift and Ellis,<sup>13</sup> Stühmer,<sup>14</sup> Gonder,<sup>15</sup> and Swift<sup>15</sup>) this combination attains its maximum curative efficiency after subjecting it to specified periods of incubation. Granting that the administration of the plain drugs in small amounts intraspinally may be free from hazard, such a procedure must be carried out in total disregard for vital prerequisites established by exhaustive research work. If the proper care is exercised in the preparation of a salvarsanized serum, its use is attended with practically no danger. In more than thirty-five hundred treatments I have seen but one severe reaction of a permanent character follow. Many patients suffer much more severe reactions following an intravenous treatment of salvarsan than they do after intraspinal treatment. In fact, I am entirely in accord with Cotton (who has given more than three thousand treatments) when he states that in many instances intraspinal treatment is actually less hazardous than intravenous.

It has further been stated that plain serum is productive of results equal to those following the use of a salvarsanized serum, although little or no tangible evidence has been submitted to support the contention. Swift<sup>17</sup> found that the Wassermann reaction and the cell count was somewhat influenced in a small number of cases. I have also found this to occur in a few cases treated in this manner,



but in my observations there was a striking absence of any clinical improvement. As a matter of fact the simple draining of the subdural space, that is, the removal of twenty or thirty cubic centimeters of fluid every five or six days, has been found to temporarily reduce the cell content, and it is well known that the Wassermann reaction occasionally becomes negative in certain titrations in the intervals between courses of treatment.

Observations of this kind are interesting and should be noted for possible "leads" in the work, but they can not logically be set up to discredit facts established by long and patient investigation. The value of intraspinal therapy in neurologic syphilis has for several years been the subject of exhaustive study by able clinicians and laboratory workers. Our curative agents are no doubt as yet imperfect, and it is highly probable that the manner of administration can be improved upon, but the observations of Fordyce, Tilney, Cotton, Draper, Amsden, Walker and Haller, Stoner, Riggs and Hammes, Gaines, Cutting and Mack, and others have at least established the fact that the method is a most valuable adjunct in combating diseases of this kind.

In previous communications<sup>18, 19, 20</sup> I have reported the results obtained from the use of a salvarsanized serum of standard strength. In the preparation of this serum I followed, and embodied the principles of, the method of Swift and Ellis, but aimed to eliminate the uncertain salvarsan content of their serum by preparing *in vitro* a serum of definite known therapeutic value. Briefly, the technic as originally described, and which has not been changed in any material way, is as follows:

Ten cubic centimeters of *clear* human serum are obtained either by centrifuging a tube of freshly drawn blood at approximately 3000 revolutions for from ten to fifteen minutes, or permitting a clot to form by letting it stand overnight. (Originally 15 c.c. was recommended, but it has since been found that the smaller amount is sufficient, and productive of equally as good results.) It is not essential that an autogenous serum be employed. Sera taken indiscriminately from patients can be used, and where a large number of patients are to be treated the sera can be pooled and divided into amounts of 10 c.c. each. Care should be taken to free the serum absolutely from fibrin and cellular elements, and to this end it is sometimes necessary to centrifuge a second time. Under no circumstances

should a serum be used that contains hemolized red blood cells. The test tube containing the serum is then placed in a water bath at body temperature until the salvarsan is ready to be added. *In preparing the salvarsan solution the greatest care must be exercised in alkalizing it.* The sodium hydroxid solution must be fresh (preferably not more than four or five days old), and only a sufficient amount added to *very faintly* alkalinize the salvarsan solution. The salvarsan solution will be more readily and accurately alkalized if the sodium hydroxid is added while the former is about body temperature. A very hot salvarsan solution requires more sodium hydroxid to faintly alkalize it, but when it is cooled down the degree of alkalinity is apparently markedly increased, and a serum charged with such a solution invariably produces a reaction (usually root pain) when given intraspinaly. The salvarsan solution should be prepared so that each cubic centimeter contains one milligram of the drug. While at first thought of minor importance, this part of the technic should be carefully considered. Unless one is familiar with laboratory work to some extent he is liable to miscalculate his dilution strengths and give more of the drug than is intended. With a 1 c.c. pipette, graduated into tenths or twentieths, the exact amount of salvarsan desired for the case under treatment is added to the ten cubic centimeters of serum, care being taken that the two solutions are at the same temperature (preferably 37.5° C.). The serum should then be gently agitated to insure thorough mixing. It is now placed in a water bath thermostat at 37.5° C. for forty-five minutes. From this it is placed in a thermostat at 56.0° C. for thirty minutes, after which it is removed from the water bath and as soon as the temperature is reduced to approximately that of the body, it is ready to be given to the patient.

Under no circumstances should a serum be given that is more than three hours old from the time it is removed from the last thermostat. The treatment is better borne, and the results are more satisfactory if the serum is used within an hour after its preparation. This is probably due to the fact that the arsenical compound can only withstand a limited amount of heat without becoming toxic and impairing its beneficial properties. In view of the unstable character of neo-salvarsan, as compared with salvarsan, the former should never be employed in this work. Furthermore Stühmer<sup>19</sup> has shown that serum from salvarsan treated rabbits possessed a more persistent

trypanosomicidal action than did serum from rabbits treated with neosalvarsan.

In paresis a relatively stronger serum is indicated than in other types of neurologic syphilis, but the maximum amount of salvarsan that can be repeatedly given with safety is one-half of a milligram. Treatments of this strength should rarely be repeated more often than every two weeks but in strengths of 0.2 or 0.3 mg. it is quite safe to make the intervals ten days, or even one week, for a series of three or four treatments, when there should be an interval of two or three weeks before proceeding. The frequency of administration and the serum strength, however, must be dependent upon the same factors that determine the judicious use of therapeutic agents generally, such as the physical condition of the patient, the character of reactions following treatment, if any, and the urgency of the case as indicated by the clinical and serobiological pictures.

The lumbar puncture for an intraspinal treatment *should never be done with the patient sitting up*. He should be placed on his side with the thighs well flexed on the abdomen. Unless the flow indicates a very low pressure in the subdural sac, I have found that the treatments are better borne if approximately one and a half times as much fluid (15 c.c.) is removed as the amount of serum to be introduced. In some instances where the fluid is under very high pressure as much as 20 c.c. should be removed. The barrel of a 20 c.c. glass syringe, used in the treatment, is then connected and lowered until it contains about 10 c.c. of fluid, when the serum is poured in and the barrel elevated to permit the mixture to slowly flow into the canal.

After the treatment it is extremely important to keep the patient absolutely quiet, preferably on his back and without pillows, for at least five or six hours, and in the recumbent position for from thirty-six to forty-eight hours. Some patients are apparently quite able to leave the bed in twenty-four hours, or even less, but I have found that, as a rule, better results are obtained by insisting upon the longer period of rest.

I will now set forth the results of treatment in fifty-five cases of general paresis, in which this serum was used in conjunction with salvarsan intravenously and mercury intramuscularly. Intravenous treatments were given only when indicated and well borne. They were usually scheduled to alternate with the intraspinal. Not infrequently some cardio-vascular or renal disorder precluded the use of

salvarsan by vein and the intraspinal treatments were relied upon entirely.

Each case of this series presented the cardinal symptoms, physical signs, and serobiologic findings of the syndrome as clinically recognized today. Care was taken to eliminate all doubtful cases that might come under the heading of cerebrospinal syphilis or syphilitic meningitis. I have tried to determine as accurately as possible the value of intraspinal treatment in *paresis*, measuring the results in terms of remissions with due regard for their duration.

Of the total number referred to, thirty-five cases were preliminarily reported in October, 1915.<sup>20</sup> As stated at that time, only five of this group were socially possible when treatment was instituted, and twenty-two had had intensive intravenous and intramuscular treatment over periods varying from six months to two years, only eight of which had had remissions, and these were from two to eight months duration. With the exception of two cases out of the thirty-five I have been able to follow all of them to date, and in order to compare the present status of this series with what it was in 1915, they will be considered separately. Twenty additional cases, that had not been under observation long enough to be included in the report at that time, will then be considered.

The results attained in the cases comprising the 1915 report were divided into three groups, as follows:

1. *Complete Clinical Remissions*.—There were twelve, or thirty-four per cent, in this group, and the average duration of the remissions established was, at that time, one year and two months. At this writing six of the twelve still remain clinically well, and five continue to pursue their former vocations in life. The average duration of the remissions now is two years and nine months. Four cases in this group, that were reported serobiologically negative have remained so. Of the remaining six cases, three have suffered partial relapses (after an average complete remission period of two years), but still remain socially possible; two have suffered complete relapses (after remissions of two years, and one year and nine months, respectively) and are rapidly deteriorating. One case has not reported back for observation but was declared to be in apparently perfect health by a relative two months ago. When last examined his remission had been clinically complete for fifteen months.

2. *Incomplete Clinical Remissions.*—This group comprised fourteen cases, or forty per cent of the total number, in which the remissions were sufficiently well established as to render the patients socially possible; that is to say, able to remain at home and to attend to their daily routine of living without attendance. Originally all of the patients in this group were totally incompetent, either confined in institutions for the insane or kept at home in the care of nurses. The average duration of the remissions at the time of the first report was twelve and one half months. At this time only seven of the original number are in as good mental and physical condition as they were then. However, their remission periods now average two years, seven and one-half months. Of the remaining seven cases four suffered complete mental and physical relapses after an average remission period of approximately two years; one died in an epileptoid seizure after a remission of eighteen months, and two failed to report back for observation, all trace of them being lost. At the last examinations the remissions were of eighteen and fifteen months duration, respectively.

3. *Cases that Failed to Show Any Appreciable Response to Treatment.*—In this lot there were nine patients, or approximately twenty-five per cent of the total. Seven of this number had had brief remissions, or showed some slight improvement in one way, or another, but none could be counted as successful cases. Four of this number have died; two have remained practically unchanged; two have slowly deteriorated, and one has sufficiently improved, without treatment of any kind, as to be socially possible.

Treatment was administered to the patients comprising Groups 1 and 2 only when there was some clinical or laboratory evidence of an impending relapse. The intensity of the treatment given in such instances was proportionate to the gravity of the situation, but if a reasonable amount failed to exert any further beneficial influence, it was discontinued altogether. From the laboratory point of view the recurrence of pleocytosis, or of increased globulin in the spinal fluid, was recognized as the forerunner of a clinical relapse even though the patient remained unchanged clinically.

The following tables will serve to summarize the results in this series (the report of October, 1915) compared with the present one (Tables I, II and III).

TABLE I  
COMPLETE REMISSIONS

OCTOBER, 1915	CASES	PER CENT	AVERAGE DURATION
	12	34.2	One year and two months.
MAY, 1917			
Unchanged.	6	17.1	Two years and nine months.
Partial relapse; still socially possible.	3	8.6	Two years. (At time of relapse.)
Complete relapse; deteriorating.	2	5.7	Two years. (At time of relapse.)
Unable to follow; reported well 2 mo. ago.	1	2.8	One year, nine months. (At time of relapse.)
			Fifteen months. (Last examination.)
Total	12		

TABLE II  
INCOMPLETE REMISSIONS

OCTOBER, 1915	CASES	PER CENT	AVERAGE DURATION
	14	40.0	Twelve and one-half months.
MAY, 1917			
Unchanged.	7	20.0	Two years, seven and one-half months.
Complete relapses.	4	11.4	Two years. (At time of relapse.)
Died.	1	2.9	Eighteen months. (At time of death.)
Lost to observation.	2	5.7	Fifteen and eighteen months. (At last examination.)
Total	14		

TABLE III  
FAILURES (NO APPRECIABLE BENEFIT FROM TREATMENT)

OCTOBER, 1915	CASES	PER CENT	SOME TEMPORARY IMPROVEMENT IN
	9	25.6	SEVEN CASES
MAY, 1917			
Unchanged.	2	5.7	
Steadily deteriorating.	2	5.7	
Died.	4	11.4	
Spontaneous remission.	1	2.8	Socially possible for past nine months.
Total	9		

Including six cases still complete, and ten in the incomplete group, the total number of remissions at this time is 16, or 45.7 per cent of the original total of thirty-five cases, and the average duration is more than two years and eight months.

Of the twenty additional cases to be included in this report, fifteen had previously received intensive intravenous and intramuscular

treatment, while five cases had not received treatment of any kind. Of the fifteen treated cases four showed negative Wassermann reactions in the blood, but all had strongly positive findings in the cerebrospinal fluid. In a number of instances more than twenty treatments of salvarsan intravenously had been given, while four patients had received in all more than thirty such treatments. There had been some clinical improvement, manifested in one way or another, in twelve of the treated cases. In four instances complete remissions had been established lasting from three to six months, but all had suffered complete relapses and failed to show any appreciable response to further intravenous treatment. A striking illustration of the inefficacy of intravenous treatment alone in some instances is afforded in the following case. A physician, forty-five years of age, had been infected fourteen years previously. At that time he had taken the orthodox mixed treatment steadily for three and a half years. He remained in apparently good health until the spring of 1911 when he developed severe headaches, dizziness, and diplopia from paralysis of the left external rectus. His blood was negative to the Wassermann reaction but a lumbar puncture showed a positive Wassermann and a "very marked increase in cells and globulin." Treatment with salvarsan intravenously and mercurial inunctions was immediately started. From May of 1911 until February, 1912, he received eighteen intravenous treatments and approximately ninety inunctions of mercury. He was also given potassium iodide at irregular intervals. His symptoms disappeared shortly after treatment was instituted and he remained in good health until October of 1912, when he had a convulsive seizure. Examination then showed fixed pupils, tremor of the hands, facial muscles and tongue, a marked speech defect and a moderate degree of memory impairment. At that time his fluid showed forty-five cells to the cubic millimeter, a marked amount of globulin and a positive Wassermann reaction in all titrations. I advised intraspinal treatment but, because the method was then comparatively new, he declined it, and, returning home, began a vigorous course of intravenous treatment. In the following year he took twenty-eight full doses of salvarsan and forty-two intramuscular injections of mercury. He improved some clinically but was able to attend to only a few unimportant details of his practice. In the month of December, 1914, he began to grow rapidly worse, having four convulsive seizures within a period of three weeks.

An examination of his fluid at that time showed fifty-eight cells to the cubic millimeter (more than he had had fourteen months previously), a marked excess of globulin and a positive Wassermann in all but the two weaker titrations, *despite the fact that he had received altogether forty-six intravenous treatments of salvarsan and a great deal of mercury* and potassium iodide. In April of 1915 he was placed upon intraspinal treatment alone, the other treatments being omitted in view of the enormous quantity he had already received and because the blood Wassermann was negative. He immediately began to improve, the epileptoid seizures stopped, and in eight weeks (having received six intraspinal treatments ranging from 1/8 to 1/2 mg.) his remission was clinically complete, the fluid showed 4 cells to the c.mm., a moderate amount of globulin, and a positive Wassermann only in 1.0 and 0.8 c.e. Subsequently he received ten additional treatments at intervals of from two to three weeks. He remained well enough to attend to the greater part of his practice until December, 1916 (a period of eighteen months), when he again began to deteriorate. Further treatment was then ineffectual but it seems reasonable to believe that in this case the specific process could have been controlled had intraspinal therapy been instituted, along with the other methods, when an involvement of the central nervous system was first recognized.

Another case illustrating the value of intraspinal treatment alone when other methods were contraindicated is of interest. A salesman 56 years of age came to my office in December, 1915. He was sent by his employers who stated that he had steadily deteriorated in efficiency for three months previously; that he was "absent minded," could not make out an accurate order slip or report his daily activities. He gave no history of infection but examination showed irregular and fixed pupils, unequal knee and ankle jerks, marked tremor of hands and tongue, and some speech defect. He was fairly clear mentally but unaware of his recent inefficiency. His blood and fluid were both corroborative of paresis. His blood pressure was 210 and the urine showed evidence of a well advanced interstitial nephritis. Attempts to treat him intravenously even with as little as 0.2 gm. of the drug met with violent reactions; choking, flushing, vomiting, and followed immediately by an increase in the pathological urinary findings. In consequence of these reactions the intravenous treatments were abandoned after two had been given. Repeated intraspinal ther-



apy was well borne and followed by no evidence of kidney or cardiovascular irritation. There was a very decided clinical improvement after the third treatment and after the fifth he was able to resume his work. He remained well enough to hold his position for nine months, after which time he again developed some mental defects and was forced to retire. While now unable to earn a livelihood, he is well enough to remain at home unattended and to look after his personal affairs alone. In this case, salvarsan intravenously would have done far greater harm than good and the clinical course would undoubtedly have been quite different but for the intraspinal treatment.

The results in this series will be summarized as in the former one, by dividing them into three groups: 1. *Complete Remissions*; 2. *Incomplete Remissions*; and 3. *Failures*.

1. In this group there are six cases, or thirty per cent of the total number. Five of the six have been able to resume their former vocations in life. The average duration of the complete remission is one year and four months. The number of treatments required to establish a remission averaged fourteen. Three patients received only intraspinal treatment. The cell and globulin content in the spinal fluid has remained practically normal during the entire period of remission in five cases, while in one there was evidence of a relapse after four months and intensive treatment was necessary to control it. None of these cases were rendered entirely negative as regards the Wassermann reaction, two remaining positive in all titrations and four remaining positive in all titrations from 0.4 c.c. to 2.0 c.c.

2. There are nine cases, or 45 per cent, in which the remissions established were incomplete, but in which the patients were made socially possible. Two patients in this group were given intraspinal treatment alone. The average duration of the remission period is one year and two months, and the number of treatments required to induce the maximum degree of clinical improvement averages nine. The cell and globulin content of the spinal fluid was rendered practically normal in only five cases while in four the globulin content failed to go below a + ("moderate excess"). The Wassermann reaction in the fluid was not influenced to any appreciable extent except in one instance where it became negative in all titrations below 0.8 c.c. All of this number were originally totally incompetent. At this time six out of nine, while unable to resume their former vocations, are able to earn enough at simple callings to contribute in a

substantial way to their support. One of the remaining three requires attendance when on the street but is quite tractable and able to care for himself when at home.

3. There are five cases, or 25 per cent of the total, that failed to respond to treatment. Two of these had manifested symptoms of the disease for less than three months, and from a clinical point of view were apparently quite favorable cases for treatment. Both showed very positive findings in the fluid, however, and both gave a decided parietic curve with the Lange colloidal gold test. Three cases were of more than one year duration and all three were well advanced both mentally and physically.

From a study of this series of twenty cases the results will be found to fairly closely parallel the results in the series of thirty-five when first reported. The two series considered together are shown in Table IV.

TABLE IV

	1915	1917	Total	Percentage
Complete Remissions.	12	6	18	32.7
Incomplete Remissions.	14	9	23	41.8
Failures.	9	5	14	25.5
Total.	35	+ 20	= 55	100.0

In those cases that have been most satisfactorily influenced the specific process is probably confined largely to the interstices and meninges. This type is no doubt a precursor of parenchymatous involvement but the prognosis is unquestionably better, provided treatment is started early and given intensively. Clinically the two types are practically indistinguishable, but with further study of the value of the Lange test we may eventually be able to accurately differentiate them, and from this determine the prognosis in a given case.

Broadly considered, intraspinal therapy, with the curative agents now at hand, may be said to be of value in true *paresis* only as a means of holding the disease in abeyance for a period dependent upon the extent of its activity at the time treatment is instituted. That it is far superior in accomplishing this, to any other treatment known today, is unquestionable. In appraising the value of the method heretofore sufficient consideration has not been given to the nature of the pathological process. We have expected too much of it. When the classical syndrome is clinically established we are dealing with atro-

phic parenchymatous degeneration of the brain tissue. With due consideration for this fact, and in view of the restraining influences exerted on the process by intraspinal treatment, its value in combating brain syphilis before irreparable damage has been done seems apparent.

The real problem is to recognize invasion of the central nervous system before even the interstitial tissue or the meninges are involved to any destructive extent. It is the consentient opinion of authorities generally that these parts are invaded prior to, or during, the secondary stage of the infection. One should therefore not wait for clinical evidence of nervous involvement, but the cerebrospinal fluid should be carefully scrutinized during, as well as subsequent to, this period. If neurologic involvement is detected at this stage, we have adequate means of controlling it, and if these are judiciously employed, *general paresis* will, in not far distant years, become a comparatively rare picture in medicine.

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## OBSERVATIONS ON TYPES OF RESPONSE IN TREATMENT OF SYPHILIS OF THE CENTRAL NERVOUS SYSTEM\*

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IN a short discussion of treatment of syphilis of the central nervous system it is practically impossible to consider all phases of the subject. With the recent simultaneous development of new methods of diagnosis and new forms of treatment, our knowledge of the results of therapy must necessarily rest upon an experimental basis. The object of this communication is, therefore, to present detailed observations in the treatment of various forms of the disease and to point out certain conclusions from these observations.

It is well established that the central nervous system is involved in all stages of the disease. While it is thought by many syphilographers that the future course of the disease is largely determined by the invasion of the nervous tissues in the early secondary period, still the various clinical pictures depend upon numerous factors, such as time since infection, amount of treatment, tissues involved, and certain unknown influences in resistance and immunity at present but little understood. In the days when nosology dominated the study of the disease, various types, such as syphilis and parasyphilis, were described. This classification was useful, and even today when combined with the more modern methods of laboratory examination, is not without value in prognosis and to a certain extent as a guide in treatment.

For convenience in classifying, the various types may be grouped under three main headings:

1. Vascular.—The essential lesion is an endarteritis, and the nervous lesion is due to disturbed circulation.

2. Exudative.—The most marked lesion is cellular thickening of the supporting membranes or perivascular spaces, with gumma forma-

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\*Read before College of Physicians, Philadelphia, February 7, 1917.

tion and subsequent mechanical injury to cortex, tracts, and intradural portions of nerves.

3. Parenchymatous.—The striking picture is tract or cortical degeneration, but in which the essential lesion is probably a chronic meningitis and perivascularitis. At least this appears to be true of the various tabetic manifestations. In paresis a true inflammation of the cortex seems to exist. This peculiarity in the paretic process probably explains the intractability of this condition to treatment.

The pessimism of many of the older neurologists in regard to permanent cure of central nervous syphilis probably arose because of their failure to take into consideration all of these factors, indeed many of the differences have been only recently appreciated. On the other hand the statement that all forms of central nervous syphilis respond equally well to intensive general medication must be the result of insufficient observation of a sufficiently wide variety of cases. By the presentation of the details of the treatment of a number of patients, I hope to prove that treatment must be individualized, and that the response in the cerebrospinal fluid is one of the most important guides to both the kind, and sufficiency of treatment.

The order in which the records are presented is determined to a certain extent by the stage of the disease. This order, however, is modified by various factors, such as clinical forms and peculiarities in laboratory findings.

Case 1 (W. E.) is an illustration of severe involvement of the meninges in a very early stage. With the appearance of headaches, even before the cutaneous manifestations, and deafness two months after the appearance of the chancre, we are justified in assuming that the eighth nerve was implicated in a basal meningitis. The results of single early injections of salvarsan are well demonstrated for although the symptoms were temporarily relieved, the essential process was not eliminated as shown by the first lumbar puncture. The ease with which the abnormal elements in the fluid may be eliminated by systematic treatment is well shown, for following eight intravenous injections of salvarsan in three months' time the fluid became practically normal. There was a simultaneous disappearance of symptoms. A year and a half of continuous intensive treatment was required, however, before the serum Wassermann reaction remained negative.

The manner in which this patient responded to treatment is fairly typical of that usually seen in early meningitis. Six out of a group

## GROUP 1.—EARLY MENINGITIS

TABLE I

W. E. Male. Age 25. Oct. 18, 1911. Primary.  
 Nov. 15. Severe headache, hyperesthesia of scalp.  
 Nov. 24. Salvarsan, amount unknown.  
 Dec. 26. Deafness, right ear; headache.  
 Jan. 22, 1912. Salvarsan, amount unknown.  
 Apr. 11. Admitted. Headache and nervousness. Physical examination negative except exaggerated reflexes and hyperemia optic discs.

DATE	BLOOD	CEREBROSPINAL FLUID			TREATMENT	
	W. R.	Cells	Noguchi Glob.	Wassermann Reaction	Salvarsan	Mercury
1912						
Apr. 16	++	190	±	0.8 c.c. ++++	3 × 0.3 gm.	
May 6 to May 20	++++	23	±	1.0 c.c. ++++	3 × 0.3 gm.	
May 22					2 × 0.6 gm. neo.	
May 29 to June 11						
June 19 to June 27	++	7	-	1.0 c.c. -	0.6 gm. neo.	4 inj. Hg. Sal.
July 2						
July 11	++++	4	-	1.0 c.c. -	5 × 0.9 gm. neo.	25 rubs
Sept. 6						
Sept. 9 to Sept. 23	++	0	-	1.0 c.c. -	6 × 0.9 gm. neo.	3 inj. Cal.
Nov. 22						
Nov. 25 to Jan. 1	++++	5	-	1.0 c.c. -	8 × 0.5 gm.	2 inj. Hg. Sal.
1913						
Apr. 8	+	1	-	1.0 c.c. -	12 × 0.5 gm.	4 inj. Hg. Sal.
Apr. 1 to May 27						
Sept. 30						
Oct. 1 to Feb. 16	-					
1914						
Feb. 16	-	1	-	1.0 c.c. -	0.5 gm.	
Apr. 27						
1915						
Feb. 3	-	6	-	2.0 c.c. -	0.4 gm.	
Feb. 15	-					
Feb. 16	-					
Feb. 19	+					
Feb. 25	+					
Mar. 1 to May 15						30 rubs
May 15	-					
1917						
Jan. 15	-	6	-	2.0 c.c. - Gold Curve: 1111100000		

of eight such cases have shown a similar response to persistent intensive general therapy. Several of them likewise showed a tendency for the symptoms to recur when early treatment was applied in a desultory manner.

Case 2 (C. W.) is an example of a true neuro relapse. The patient did not have any symptoms of central nervous origin until an interval had elapsed after the first course of salvarsan. Then a clinical picture appeared which pointed to severe and extensive involvement of the basal meninges. The general nervous symptoms were as severe as often seen in the second stage of tuberculous meningitis, and the cerebrospinal fluid showed a pleocytosis more intense than is often present in this disease.

TABLE II

C. W. Male. Age 34. May 2, 1911. Primary.  
 May 27. Secondaries.  
 June 9 to 24. 1.5 gm. salvarsan.  
 July—August. 6 inunctions and 12 inj. Hg.  
 Aug. 19. Stiffness of neck, headache, dizziness.  
 Aug. 23. Deafness, facial paralysis.  
 Sept. 23. Admitted. Headache, dizziness, mental dullness, exaggerated reflexes, deafness, facial paralysis.

DATE	BLOOD	CEREBROSPINAL FLUID			TREATMENT	
	W. R.	Cells	Noguchi Glob.	Wassermann Reaction	Salvarsan	Mercury
1911						
Sept. 23	++++	1094	++	0.2 c.c. ++++	3 × 0.2 gm.	
Sept. 27 to Oct. 12	++++	118	+	0.2 c.c. -	7 × 0.2 gm.	
Oct. 16	+++	60	+	1.0 c.c. ++	2 × 0.2 gm.	
Oct. 19 to Nov. 29	++					
Dec. 5						
Dec. 7 to Dec. 14						
1912						
Jan. 8 to Jan. 15						2 inj. Hg. Sal.
Jan. 21	-	9				6 inj. Hg. Sal.
Jan. 21 to Mar. 4						
Mar. 8	+	46	+	1.0 c.c. +	6 × 0.3 gm.	
Mar. 12 to Apr. 16					3 × 0.3 gm.	
Apr. 18	-	11	±	1.0 c.c. -		
May 7 to May 28		8	-	1.0 c.c. -		6 inj. Hg. Sal.
May 31					0.9 gm. neo.	
July 16 to Oct. 7	+					
Oct. 19	++++	22	-	1.0 c.c. -	7 × 0.9 gm. neo.	
Oct. 26						
Oct. 26 to Dec. 14						
1913						
Jan. 13 to Mar. 25						7 inj. Cal.
Apr. 12	+	6	+	1.0 c.c. -	3 × 0.9 gm. neo.	
Mar. 29 to Apr. 19					6 × 0.5 gm.	
Apr. 26 to June 21						6 inj. Hg. Sal.
June 29 to Aug. 18	-	3	±	1.0 c.c. -	16 × 0.5 gm.	
Aug. 30						
Sept. 13 to Feb. 21						
1914						
Feb. 21	-	6	±	1.0 c.c. -	9 × 0.5 gm.	
Apr. 25 to Sept. 7						
1915						
Jan. 21	-					
June 12	-			2.0 c.c. -		
1916						
July 3	-	7	-	2.0 c.c. -	Gold Curve: 0000000000	
Oct. 23	-				0.3 gm. Sal. provocative	
Oct. 25	-					
Oct. 28	-					
Oct. 30	-					
Nov. 2	-					
Nov. 7	-					

The clinical improvement and diminution in abnormal elements in the cerebrospinal fluid promptly followed the administration of repeated injections of 0.2 gm. of salvarsan. The diminution in pleocytosis was slower than in Case 1. Twice, March 8, and October 26, 1912, there was an increase in the cell count while the patient was receiving intramuscular injections of mercury. This fact is of especial interest in connection with the occurrence of his first attack during

intensive mercurial treatment. Only by persistent application of salvarsan over a period of three years with occasional short courses of mercury, could the spinal fluid be brought to a permanent normal condition. The persistence of a normal cerebrospinal fluid and of a negative serum Wassermann reaction during two years without treatment, and the negative results of provocative treatment seem to indicate that the disease is completely eradicated. This case illustrates how important the repeated examinations of the cerebrospinal fluid may be, for the recurring pleocytosis under mercury served as an indicator of the necessity for salvarsan. The superiority of salvarsan over mercury is also elicited. This is doubtless the type of case which terminated fatally from meningitis in the presalvarsan era.

Case 3 (W. R.)\* is an example of how apparently a lesion of the central nervous system may be a focus from which the serum Wassermann reaction may repeatedly relapse. Three times during a period of two and one-half years the reaction reappeared in the serum when treatment was discontinued. The patient was able to take mercury in large quantities, and each subsequent course of treatment was more intensive than the last. The only symptoms or signs of central nervous system involvement were very active reflexes. Still in October, 1914, a lumbar puncture revealed the presence of an active meningitis. The form of treatment was then changed to less intense general therapy with the addition of intraspinal injections of the patient's own serum obtained after intravenous salvarsan injections. Under this new mode of treatment, there was steady improvement in the condition of the cerebrospinal fluid until it became entirely normal. Two more combined treatments were given after which all drugs were discontinued. Contrary to the experience in the first two years the blood Wassermann reaction has not relapsed and, moreover, the fluid has remained normal.

This case seems to prove that in certain patients even in the secondary period intensive general treatment may not be sufficient to control an infection in the cerebrospinal axis, and that intraspinal therapy in addition may be necessary.

These three cases illustrate the variations in response in the secondary period. The first was easily influenced by salvarsan intravenously, and there was no tendency to a relapse when treatment was discontinued. The second was more resistant and relapsed when

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\*The patient was under the care of Dr. A. R. Stevens, who kindly furnished the notes.



TABLE III

W. R. Male. Age 34.

DATE	BLOOD		TREATMENT					
	W. R.		Salvarsan	Hg. Sal. Intramuscular	HgCl <sub>2</sub> pills p. o.			
1912		Primary lesion Rash. Adenopathy. Mucous patches.						
Jan. 29								
Mar. 29								
30 to								
June 25				3 inj.	13 inj.			
July 29	-			1.65 gm.	Total: 1 gm.	2.5 gm.		
Sept. 19	++							
Oct. 5 to				7 inj.	18 inj.			
1913				Total:	Total: 3.3 gm.	9.4 gm.		
Mar. 29				4.2 gm.				
May 21	-							
July 16	+++							
23	+++ ±							
28 to					6 inj.			
Sept. 20	-				Total: 0.8 gm.	2.6 gm.		
20 to				7 inj.	8 inj.			
Nov. 28				4 gm.	Total: 1.3 gm.	2.4 gm.		
28 to				4 inj.	10 inj.			
1914			Total:	Total: 2 gm.	2.6 gm.			
Feb. 25			2.4 gm.					
25 to								
May 18			3 inj.	8 inj.				
July 7	-		1.7 gm.	Total: 1.6 gm.	3.3 gm.			
Aug. 10	++++							
12 to					2.6 gm.			
Oct. 6								
		CEREBROSPINAL FLUID			TREATMENT			
		Cells	Glob.	W. R.	Gold	Sal. Intrav.	Serum Intrasp.	HgCl <sub>2</sub> pills
Oct. 9		65	+	0.4 c.c. ++++				
24						0.6 gm.	20 c.c. 40%	
Nov. 6						0.6 gm.	30 c.c. 45%	
Dec. 4		30	++	0.8 c.c. ++++		0.6 gm.	52 c.c. 50%	
1915								
Jan. 8						0.6 gm.		
29			+	1.0 c.c. ++++		0.6 gm.	32 c.c. 40%	14.6 gm.
Mar. 26 to						0.5 gm.		KI 133 gm.
May 1								
June 4		20		0.8 c.c. ++++		0.6 gm.	40 c.c. 50%	
July 9						0.5 gm.	40 c.c. 50%	
30						0.6 gm.	40 c.c. 50%	
Aug. 13		5	+++	1.0 c.c. -		0.6 gm.	40 c.c. 50%	
Oct. 1			-	2.0 c.c. ++++		0.5 gm.	40 c.c. 50%	
29				2.0 c.c. ++++		0.6 gm.	36 c.c. 50%	
Nov. 19						0.45 gm.	40 c.c. 50%	
Dec. 18		3	+	1.5 c.c. ++++		0.35 gm.	36 c.c. 50%	5.6 gm.
1916								
Jan. 28			-	2.0 c.c. -	00000	0.4 gm.	40 c.c. 50%	
Feb. 5					00000			
Mar. 17			-	2.0 c.c. -		0.4 gm.	30 c.c. 40%	
May 20	-	3	-	2.0 c.c. -	00000			
Aug. 1	-	5	-	2.0 c.c. -	00000			
Nov. 26	-	2	-	2.0 c.c. -	00000			

mercury was substituted for salvarsan. In the third the most intensive general application of salvarsan, mercury, and iodides was not sufficient to eliminate the meningeal lesion. Only after intraspinal injection of serum was the active syphilitic lesion eliminated.

In all the patients the only clinical residuum of their nervous lesion is the persistence of very active deep reflexes. It is conceivable that as a result of the former inflammatory process there may be a certain amount of scarring which has affected the upper motor neuron.

GROUP II.—LATER FORMS OF CENTRAL NERVOUS SYPHILIS OF THE  
EXUDATIVE TYPE

TABLE IV

M. P. Male. Age 26. Syphilitic meningitis. Retrobulbar neuritis and atrophy.  
Jan. 5, 1909. Chancre, spirochete present.  
Jan. 5 to Mar. Arsacetin 30 inj. hypo.  
Mar., 1909, to Mar., 1910. Hg. Intramusc. 100 inj.  
Mar. to July. Pills 100.  
July, 1910, to July, 1911. Pills and KI.  
July, 1911. Salvarsan intramuscularly, suppuration.  
Jan., 1912. Salvarsan intramuscularly.  
July, 1912. Sodium cacodylate 18 inj. Fullness in head,  
flashes of light, pain in legs.  
Oct. 20, 1912. Admitted. Retrobulbar neuritis and atrophy,  
narrowing of visual fields.

DATE	BLOOD	CEREBROSPINAL FLUID			TREATMENT		
	W. R.	Cells	Glob.	Wassermann Reaction	Salvarsan gm.	Hg.	
1912 Oct. 25 27 to 1913 Jan. 23 Jan. 23	-	40	+	1.0 c.c. -		Hg. Sal.-14 inj. Total 0.8 gm. KI 4 gm. per day	Visual fields normal.
Jan. 28	-	59	±	0.6 c.c. + + + +	Neo. 0.6		
Feb. 4	±				" 0.9		
11	±				" 0.9		
15	++++				" 0.9		
22	++++				" 0.9		
Mar. 1	++++				" 0.9		
8	++				" 0.9		
15	+++				" 0.9		
22					Sal. 0.5		
Apr. 4 to June 16 21	+++	4	-	1.0 c.c. -		Hg. Sal. 0.5 gm. Total	Fundi and visual fields normal.
28					Sal. 3 × 0.4 gm.		
July 12 Sept. 18 1914	++	7	-	2.0 c.c. -	Sal. 0.5 gm.		
Jan. 6 to Feb. 9 23	+				5 × 0.5 gm.	Hg. Sal. Total: 0.5 gm. hypo.	Fundi normal color, arteries narrow. Fields normal.
May 25	-						
1915 June 21	-	1	+	2.0 c.c. -			

Case 4 (M. P.) is an example of a patient in whom the first nervous symptoms appeared nearly four years after infection. For the first two years he was under the care of Professor Milian, of Paris. During this time he received fairly intensive antisyphilitic treatment. During the eighteen months before admission to the Rockefeller Hospital, his treatment was more desultory in character. When first seen he had evidently a fairly active meningitis and retrobulbar neuritis with much narrowing of the visual fields. Because of his previous intensive arsenic treatment, it was felt that the effect of mercury and iodides should be tested before resorting again to an arsenical. For this reason the patient received mercury and iodides for three months with marked improvement in the condition of the visual fields, but at the same time, the cerebrospinal fluid showed no tendency to become normal. Following a course of full doses of neosalvarsan, and a short course of mercury intramuscularly, the cerebrospinal fluid became normal, the visual fields remained normal, and the fundi showed no abnormality except slight narrowing of the arteries. The provoking of a strong Wassermann reaction from a negative phase during the course of neosalvarsan is noteworthy. Because of the persistence of the Wassermann reaction in the blood serum, treatment was continued for another ten months. The patient then disappeared from observation, but upon his return a year later it was found that his general condition was normal and that the only abnormality in the cerebrospinal fluid was a slight increase in globulin. This persistence of excess globulin has been seen in many cases in whom all other pathological elements of the cerebrospinal fluid were entirely lacking. This case is an illustration of the fact that it is safe to use large and repeated doses of salvarsan in patients with marked involvement of the optic nerve, and also that the exudative type frequently responds to persistent general medication.

Case 5 (D. Y.). This is an example of the marked exudative type of lesion occurring many years after infection. It is probable from the history of the case that the patient contracted a marital infection at least twenty years ago. Except for headaches she had never suffered symptoms referable to disease of the central nervous system until two months before admission. At the time of the first examination, both the clinical findings and the cerebrospinal fluid gave evidence of a marked increase in intracranial pressure. In this type of case we feel that it is wise to introduce treatment with mercury and

TABLE V

D. Y. Female. Age 51. Syphilis of cerebral meninges. Infection (?).  
 Oct. 10, 1915. Headache, weakness of left leg and left face, thickness of speech, improved. For past 2 weeks progressive stupor, headaches, weakness.  
 Nov. 30, 1915. Admitted. Disorientation. Rigid neck, double choked disc, exaggerated reflexes, incontinence of urine, fever.

DATE	BLOOD	CEREBROSPINAL FLUID				TREATMENT		
	W. R.	Cells	Glob.	W. R.	Gold	Sal. gm.	Hg. gm.	KI gm.
1915 Dec. 2	++++	161	++	0.6 c.c. +++++				
4-17	++++					0.25	11 rubs	229
17-28	++++					0.3	3 rubs	103
30 to Jan. 8	++++	50	+	2.0 c.c. +++++		0.3		
15 Feb. to June			Discharged much improved.				Rubs—14 per mo. for 4 mos.	"some"
June to Dec. 17			Readmitted.	Anemia.	Gastric 11221	ulcer.	No treatment	
Dec. 19	++++	4	±	2.0 c.c.	00000			

large doses of iodides before resorting to salvarsan, in order to eliminate the possibility of a Herxheimer reaction. In one month's time there was a remarkable improvement in the clinical signs, a diminution in the choking of the discs, and a very gratifying improvement in the condition of the cerebrospinal fluid. After six weeks of treatment the patient insisted upon going home and continued treatment there for four months. Treatment was then stopped and after two or three months, there were symptoms pointing to the presence of a gastric ulcer. She was readmitted in December, 1916, with headaches, severe anemia, vomiting, and hematemesis. It was thought that this might be due to a gastric crisis, but further investigation confirmed the diagnosis of gastric ulcer, and on Lenhart's diet, and after two transfusions, the headaches disappeared and the patient's condition was much improved. At the time of her second admission, the cerebrospinal fluid was normal except for a slight globulin excess and a very weak luetic type of gold curve.

The case is a striking example of satisfactory improvement in the cerebrospinal fluid and clinical symptoms which was effected largely by the use of mercury and iodides.

Case 6 (I. C.). While the exact time of infection can not be determined in this case, it was probably about eleven years before admission. The case was interesting because of the uncertainty in diag-

TABLE VI

I. C. Female. Age 30. Cerebral syphilis 3 mos. Infection (11 yrs.?).  
 Oct., 1916. Convulsions, unconsciousness followed by strabismus and  
 diplopia.  
 Dec. 26, 1916. Admitted. Unequal pupils. Ptosis of right lid. Strabias-  
 mus. Right choked disc, left optic neuritis. Left  
 facial paralysis.

DATE	BLOOD	CEREBROSPINAL FLUID				TREATMENT			
	W. R.	Cells	Glob.	Wassermann Reaction	Gold	Intrav. Sal.	Intrasp. serum	Hg. gm.	KI gm.
1916 Dec. 28 to Jan. 8	+++	10	++	1 c.c. ++++	55555 42100			HgCl <sub>2</sub> 5×0.012	
11	+++							4 rubs	56
18	++++	2	+	2 c.c. +		0.1 gm.			} 158
25	++++	4	+	2 c.c. -	11232 11000	0.1 gm. 0.25 gm.	15 c.c. 100%		

nosis. With an initial symptom of convulsions and unconsciousness, the diagnosis of paresis was highly suggestive. The physical examination, however, revealed a condition which was more easily explainable by a diffuse basilar process involving both optic nerves, the oculomotor nerves on both sides and the left facial nerve. The low cell count was unusual with extensive meningitis. The gold curve, however, was of a typical paretic type. As with the former patient, treatment was instituted by means of mercury and iodides. Because of salivation after a short course of mercury, small doses of salvarsan were given. After three weeks of treatment there was a marked improvement in the cerebrospinal fluid and after four weeks the cell count was normal, the globulin less and the Wassermann reaction negative. However, because of the initial gold curve of the paretic type, it was felt that the most intensive treatment should be instituted at once, hence intraspinal injections of serum were given. The treatment was followed by a disappearance of the strabismus, marked improvement in the ophthalmoscopic picture, and general clinical betterment. Both the clinical improvement and the tendency of the cerebrospinal fluid to become normal, have been comparable in rate to that usually seen in exudative syphilis. In fact, had it not been for the paretic gold curve, we would not have hesitated to make a diagnosis of basilar meningitis. The rapid reversal of the gold curve towards the luetic type moreover confirms this diagnosis.

These three cases illustrate how well patients suffering from central nervous syphilis of the exudative type respond to general treatment. This response is manifest not only by clinical improvement, but by a rapid disappearance of the abnormal elements in the cere-

brospinal fluid. Whether a paretic type of gold curve, as seen in Case 6, will alter the prognosis, is a question for the future to decide.

#### GROUP III.—TABETIC TYPE

In *tabes dorsalis*, new problems confront us. It is probable from the history of many of these patients that even before the appearance of clinical symptoms, an inflammatory condition of the meninges has existed for years. It is only after sufficient number of tracts or nerves have become involved to call forth symptoms that the patient's attention is directed towards the true nature of his disease. Certain cases seem to be spontaneously arrested and occasionally the cerebrospinal fluid is practically normal. In such patients there is often no further advance in clinical signs or symptoms. On the other hand, in the majority of patients, the condition of the cerebrospinal fluid points to an active inflammation, and the disease is progressive in nature. Because the active part of the disease manifests itself mostly in the cord and surrounding meninges, this condition is most favorable to local therapy applied by means of lumbar puncture. However, every patient does not require intraspinal therapy; many of them respond satisfactorily to general treatment.

Case 7 (J. F.) is an example of this response. He had suffered from "rheumatic pains" in the legs for over ten years, and was known to have had sluggishly reacting pupils, and diminished knee jerks in 1904. In 1912 he obtained considerable relief following a course of mercury injections. For four months he has had vertigo, weakness, and numbness in the left arm and both feet. On examination he showed Argyll-Robertson pupils, slight deafness in left ear, a band of hypoesthesia and hypoalgesia about the chest; deep pain sensation lost in tendo Achilles and in right testicle; slight ataxia in legs; slight Romberg; triceps, patellar and Achilles reflexes absent. The cerebrospinal fluid indicated an active meningitis. He was easily poisoned by salvarsan in large doses or when too frequently repeated, nevertheless, moderate treatment soon brought the cerebrospinal fluid to normal. Because of the patient's sensitiveness to salvarsan, subsequent injections have been given at longer intervals. In January, 1917, after an interval of six months without treatments, there was some return of the pains and an increase of tingling and numbness of the left arm and leg. A physical examination showed no objective increase in the signs of *tabes*, but an examination of the cerebrospinal

TABLE VII

J. F. Male. Age 64. Tabes Dorsalis. 10 years (?)  
Syphilis (?).

DATE	BLOOD	CEREBROSPINAL FLUID			TREATMENT
	W. R.	Cells	Glob.	Wassermann Reaction	Salvarsan Intravenously
1914					
Oct. 28	++++	23	+	0.4 c.c. ++++	0.3 gm.
31					0.35 gm.
Nov. 12	++++				0.5 gm.
28	++++				0.4 gm.
Dec. 12	++				0.4 gm.
29					
1915					
Feb. 4					0.5 gm.
Mar. 20	++++	6	±	1.0 c.c. -	0.3 gm.
Apr. 16	+++				0.3 gm.
June 20	++++				0.3 gm.
Oct. 26	+++				0.3 gm.
Nov. 23	++++				0.3 gm.
1916					
May 17		4	-	2.0 c.c. -	0.3 gm.
June 7	++				0.3 gm.
30	±				0.3 gm.
July 21					0.3 gm.
1917					
Jan. 19	+				0.3 gm.
Feb. 16	+	20	±	2.0 c.c. +++	1112100000 Gold

fluid indicated a return of the meningitis. Even though the abnormal elements were not so marked as at the time of the original examination, they indicated that the disease was still present in the cerebrospinal axis, and hence treatment has been resumed. The patient, however, has been able to resume his work which previous to treatment he could attend to only occasionally.

While in some cases general treatment alone may be sufficient completely to arrest the progress of the disease both from the clinical and laboratory point of view, in other cases some additional form of therapy seems to be required.

Case 8 (G. M.) is an example of this. Patient's symptoms of tabes began in 1914 at which time he received salicylate of mercury and neosalvarsan. Upon admission to the Presbyterian Hospital Dispensary in 1915, he showed signs of an early tabes. Under mercury intramuscularly and iodides there was evidently no advance in the symptoms, until suddenly in the early part of 1916 when a Charcot's knee joint appeared. Upon admission to the hospital, he showed incomplete Argyll-Robertson pupils, hypotonia of the knees and hips, effusion into the right knee joint, hypoaesthesia in both legs, pain conduction delayed in the legs, deep pain sensation much diminished in the right tendo Achilles, but present in the left. Sense of position

TABLE VIII

G. M. Male. Age 35. Tabes Dorsalis. Duration (?).  
Tabetic arthropathy, 2 mos. Syphilis, 11 yrs.

DATE	BLOOD	CEREBROSPINAL FLUID				TREATMENT		
	W. R.	Cells	Glob.	Wassermann Reaction	Gold	Sal. Intrav.	KI	Hg.
1914								
1915 Mar.	++++	23	-	0.6 c.c. ++++		Neo. 4 inj.	KI	
Apr. to	++++						"	
1916							"	
Mar.							"	Hg. Sal. 2 gm.
Mar. 4	0	4	+	0.6 c.c. ++++				30 hypo.
18	0					0.35 gm.		
31	+					0.3		
Apr. 17	+					0.4		
May 8	0					0.4		
23	++					0.4		
June 6						0.25		
20	++	7	+	1.0 c.c. ++++		0.3		
July 12	0					0.3		
26	0					0.3		
Aug. 8	0					0.3		
24	+					0.33		
Sept. 9	++					0.3		
23	++					0.2		
Oct. 7	++					0.4		
Nov. 4	++					0.25		
18						0.3		
Dec. 2	+	29	±	0.6 c.c. ++++	11122 10000			

lost in the ankles and toes. Some incoordination in legs; deep reflexes present in arms and legs. His cerebrospinal fluid contained only four cells to the cubic millimeter, but the Wassermann reaction was as intense as one year previously. After nine months' treatment with salvarsan the Wassermann reaction is present in the same strength, and there is an increase of pleocytosis. There has been no advance in symptoms, and as a brace has been applied to the leg, the arthropathy is no more marked. It is evident, however, that the active inflammatory condition is not subsiding.

It was because of a similar lack in response to general therapy that we\* originally sought some additional form of treatment. As it had previously been shown that the serum of salvarsan treated patients had some general therapeutic effect, it was decided to determine whether intraspinal injections of this serum would be beneficial in a condition like tabes dorsalis. In order to submit this theory to the severest test the patient was first treated only intraspinally.

Case 9 (C. H. L.) is an example of the effects which may be secured from the intraspinal injection of serum alone. The patient's syphilitic infection occurred thirty years previously. He had had symp-

\*Swift, Homer F., and Ellis, A. W. M.: Jour. Am. Med. Assn., 1911, lvii, 2051; Arch. Int. Med., 1913, xii, 311.



TABLE IX

C. H. L. Age 50. Tabes Dorsalis, 10 years.  
Syphilis, 30 years.

DATE	BLOOD	CEREBROSPINAL FLUID			TREATMENT	
	W. R.	Cells per c.mm.	Noguchi Glob.	Wassermann Reaction	Intravenous	Intraspinal Other Patients' Serum
1911						
Oct. 25	-	42	+++	0.2 c.c. +++++		
Oct. 30		41	++	0.2 c.c. +++++		25 c.c. of 40%
Nov. 6		40	++	0.2 c.c. +++++		20 c.c. of 40%
Nov. 18		50	++	0.4 c.c. +++++		22 c.c. of 40%
Dec. 3	-	18	++	0.4 c.c. +++++		26 c.c. of 50%
Dec. 12		17	++	0.2 c.c. +++++		30 c.c. of 50%
Dec. 28		15	++	0.8 c.c. +++++		25 c.c. of 40%
1912						
Jan. 6		15	++	0.2 c.c. +++++		25 c.c. of 40%
Jan. 12		10	++	0.4 c.c. +++++		30 c.c. of 50%
Jan. 23		14	++	1.0 c.c. ±		26 c.c. of 50%
Jan. 31		16	+	1.0 c.c. +		30 c.c. of 50%
Feb. 7		17	+	1.0 c.c. ++		30 c.c. of 50%
Mar. 4	-	15	+	1.0 c.c. ++		
Apr. 10		10	±	1.0 c.c. +		
Apr. 16 to	-				Salvarsan 5 × 0.3 gm.	
May 14	-					
May 14		19	+	1.0 c.c. +		
Sept. 24	-	8	±	1.0 c.c. -		
1913						
Mar. 28	-	5	-	1.0 c.c. -		
June 21		2	-	1.0 c.c. -		
1914						
July 19	-	3	-	2.0 c.c. -		
1915						
July 3	-	3	±	2.0 c.c. -		

toms of tabes, such as lightening pains and numbness in the legs for the past ten years, and for six months previous to treatment had vomited daily. On physical examination, he showed evidences of a fairly advanced tabes with marked superficial and deep sensory disturbances, Argyll-Robertson pupils, diminished hearing and absence of knee jerks, one ankle jerk and much diminished tendon reflexes in arms. The treatment caused a steady diminution in all the abnormal elements in the cerebrospinal fluid. When the fluid was almost normal, five intravenous injections of salvarsan were given and then treatment was discontinued. He returned to his work and for three years the cerebrospinal fluid has remained normal. Because of similar results in several tabetics, we felt that beneficial effects were to be expected from intraspinal injections of autosalvarsanized serum.

The question naturally arose as to whether intraspinal injections of normal serum might not have a similar effect. This was tested in several patients in some of whom it was found that the abnormal elements in the cerebrospinal fluid would disappear under intraspinal injections of normal serum alone. It then remained to be determined

TABLE X

J. H. M. Age 44. Tabes Dorsalis, 2½ years. Syphilis, 14 years.

DATE	BLOOD	CEREBROSPINAL FLUID			TREATMENT		
	W. R.	Cells per c.mm.	Noguchi Glob.	Wassermann Reaction	Intravenous	Intraspinal	
1914							
Jan. 27	++++	100	+	0.2 c.c. ++++		30 c.c. of 50%	Normal Serum
Feb. 2	++++	69	+	0.4 c.c. ++++		30 c.c. of 50%	" "
Feb. 16	+++	20	±	0.6 c.c. ++++		30 c.c. of 50%	" "
Mar. 2	++++	25	+	0.4 c.c. ++++		30 c.c. of 50%	" "
Mar. 16	++++	14	+	0.4 c.c. ++++		30 c.c. of 50%	" "
Mar. 30	++++	25	+	0.4 c.c. ++++		30 c.c. of 50%	" "
Apr. 13	++++	23	±	0.6 c.c. ++++		30 c.c. of 50%	" "
Apr. 29		22	+	0.4 c.c. ++++		30 c.c. of 50%	" "
May 29	+++	43	+	0.4 c.c. ++++		30 c.c. of 50%	Sal. Serum
June 1	+++	18	+	0.6 c.c. ++++		30 c.c. of 50%	" "
June 22	+++	10	+	0.8 c.c. ++++		30 c.c. of 50%	" "
July 6	+++	10	+	0.6 c.c. ++++		40 c.c. of 50%	" "
July 20	+++	8	+	0.8 c.c. ++++		38 c.c. of 50%	" "
Aug. 3	+++	14	+	2.0 c.c. ++++		40 c.c. of 50%	" "
Aug. 24	+++	20	+	1.0 c.c. ++++		40 c.c. of 50%	" "
Sept. 7	+++	10	+	0.8 c.c. ++++		40 c.c. of 50%	" "
Oct. 12	++++	3	+	0.8 c.c. ++++	Sal. 0.5 gm.	40 c.c. of 50%	Own Serum
Oct. 26	++++	10	+	1.0 c.c. ++++	" 0.5 gm.	40 c.c. of 50%	" "
Nov. 9	++++	5	±	1.0 c.c. ++++	" 0.5 gm.	40 c.c. of 50%	" "
Dec. 7	++	5	±	1.0 c.c. ++++	" 0.5 gm.	40 c.c. of 50%	" "
Dec. 21	++++	4	-	1.0 c.c. ++++	" 0.5 gm.	40 c.c. of 50%	" "
1915							
Jan. 4	++++	3	+	0.8 c.c. ++++	" 0.5 gm.	40 c.c. of 50%	" "
Jan. 18	++++	3	±	0.8 c.c. ++++	" 0.5 gm.	40 c.c. of 50%	" "
Feb. 1	++++	3	±	1.0 c.c. ++++	" 0.5 gm.	40 c.c. of 50%	" "
Feb. 15	++++	4	-	1.0 c.c. ++++	" 0.5 gm.	40 c.c. of 50%	" "
Mar. 1	++	3	+	0.8 c.c. ++++	" 0.5 gm.	40 c.c. of 50%	" "
Apr. 26	++++	12	+	0.6 c.c. ++++	" 0.5 gm.	40 c.c. of 50%	" "
May 10	++++	1	±?	0.4 c.c. ++++	" 0.5 gm.	40 c.c. of 50%	" "
May 24	+	2	+	0.8 c.c. ++++	" 0.5 gm.	40 c.c. of 50%	" "
June 21	++	3	±	2.0 c.c. +	" 0.5 gm.	40 c.c. of 50%	" "
July 7		4	+	2.0 c.c. -			

whether salvarsanized serum was more potent than normal serum. The results of such an investigation are shown in Case 10 (J. H. M.).

This patient had chaneroid fourteen years before admission. No secondaries. Two and one-half years ago, numbness in fingers and toes, Argyll-Robertson pupils, absence of knee jerks. During two previous years patient had received two courses of mercury injections and much potassium iodide, as well as three injections of salvarsan intravenously. On admission he had Argyll-Robertson pupils, diminished hearing, slight patchy hyperalgesia, slightly ataxic gait, definite Romberg, sluggish deep reflexes in arms, and absence of deep reflexes in legs. After seven intraspinal injections, of 50 per cent normal serum, the cell count dropped to between 20 and 25, the number of cells remaining practically the same during the latter half of this course of treatment. The globulin remained the same, the Wassermann reaction was only slightly weaker. After eight injections of salvarsanized serum obtained from other patients, the cells dropped

to about 10 to the cubic millimeter. Here the drop occurred shortly after the institution of salvarsanized serum injections; the globulin remained the same, but the Wassermann reaction decreased to half its original strength. The institution of combined intravenous injections of salvarsan, and intraspinal injections of patient's own serum, caused a further drop of cells to normal, and a weakening of the globulin and the Wassermann reaction. It required, however, fourteen injections of each before the reaction in the spinal fluid became negative. The increase in the pleocytosis and Wassermann reaction while the treatment was discontinued between March 1 and April 14, 1915, is noteworthy. The renewal of treatment, however, led to rapid diminution in the strength of the Wassermann reaction in the fluid as well as in the blood serum. The result in this case seemed to indicate that salvarsanized serum is more potent than normal serum, and that the combined intravenous and intraspinal treatments are more active than either form alone.

TABLE XI

C. L. V. Age 35. Tabes Dorsalis, 6 years. Syphilis, 16 years.

DATE	BLOOD	CEREBROSPINAL FLUID			TREATMENT	
	W. R.	Cells per c.mm.	Noguchi Glob.	Wassermann Reaction	Intravenous	Intraspinal Serum
1910 Nov. 10 to 1911 Jan. 10	++++				16 injections HgCl <sub>2</sub> intramuscularly	
Jan. 16	++	125	++	0.2 c.c. -	Salvarsan 0.2 gm.	
25	++				" 0.3 gm.	
Feb. 8	++				" 0.36 gm.	
13		150	±	0.2 c.c. -		
Feb. 15 to Aug. 20	+				Mixed Treatment by mouth	
Aug. 21	+	63	+	0.2 c.c. ± ?	Salvarsan 5 × 0.2 gm.	
Aug. 26 to Sept. 22	±					
22		26	±	0.2 c.c. -		
Nov. 24					" 0.2 gm.	
Dec. 1	±	50	+	1.0 c.c. +	" 0.2 gm.	18 c.c. of 50%
Dec. 11	±	20	+		" 0.2 gm.	30 c.c. of 50%
Dec. 18	±	20	±	1.0 c.c. +	" 0.2 gm.	20 c.c. of 40%
1912 Jan. 5	-	12	±	1.0 c.c. +++	" 0.3 gm.	30 c.c. of 40%
12	-	4	-	1.0 c.c. +	" 0.3 gm.	30 c.c. of 50%
15	-				" 0.2 gm.	
20		5		1.0 c.c. ± ?		
July 9	-	2	-	1.0 c.c. -		
Sept. 10	-	1	-	1.0 c.c. -		
May 15	-	3	-	1.0 c.c. -		
1914 Feb. 2	-	Not counted	±	2.0 c.c. -		
Aug. 1	-	3	-	2.0 c.c. -		
1915 June 24	-	1	-	1.0 c.c. -*		

\*Not tested with 2 c.c.

After it was established that intraspinal injections alone were of benefit, it was desirable to determine whether the combined form of treatment was more effectual than the intravenous alone. In Case 11, this fact seems to be established. Case 11 (C. L. V.)\* was admitted January 10, 1911, with a history of a genital ulcer sixteen years previously. For past six years increasing lightening pains in legs, in the past two years loss of sense of position in feet and legs and increasing ataxia; nine months ago developed a Charcot hip. On admission patient had incomplete Argyll-Robertson pupils, very ataxic gait, hypotonia of hips and marked hypoaesthesia over lower chest and upper abdomen, entire loss of sense of position in lower extremities, deep reflexes present in arms, absent in legs. At the time of admission he was so weak and ataxic that he required two canes as well as the assistance of some other person in order to walk. Even though under the influence of mercury, he showed 125 cells and a heavy globulin in the spinal fluid. After the first three injections of salvarsan there was distinct subjective improvement and a gain in weight; the pleocytosis, however, was more marked than in the beginning, the globulin less. Mixed treatment by mouth reduced the number of cells, and further salvarsan treatment caused the cells to drop to 26. Unfortunately, during the first eight months of observation only the smaller quantities of cerebrospinal fluid were used for the Wassermann reaction, hence the cell count and globulin are the best criteria for judgment of the effects of treatment at this time. After the course of salvarsan was discontinued six weeks, the number of cells had risen to 50. The addition of intraspinal to intravenous treatment caused a rapid approximation to normal in the cerebrospinal fluid. At this time the patient also stated that subjectively his improvement had been more marked than at any previous time. For three and one-half years without treatment the cerebrospinal fluid remained normal and there was no advance in the patient's tabetic symptoms.

The importance of treating a patient with tabes until the cerebrospinal fluid becomes normal and remains so is well illustrated in Case 12 (O. F.). Ten years before admission he had an indurated genital ulcer but no secondaries. At this time mercury pills were administered for three months. Four years ago he was injured in a

\*In this and subsequent cases the intraspinal treatments consisted of injections of the patients' own serum obtained in one-half to one hour after intravenous injections of salvarsan.

TABLE XII

O. F. Age 32. Tabes Dorsalis, 3½ years. Syphilis, 10 years.  
Improvement, relapse, improvement.

DATE	BLOOD		CEREBROSPINAL FLUID			TREATMENT	
	W. R.	Cells per c.mm.	Noguchi Glob.	Wassermann Reaction		Intravenous	Intraspinal Serum
				Liver Antigen	Cholesterol Heart Antigen		
1911							
Apr. 4	++++	27	++	0.2 c.c. -		Salvarsan 5x0.2 gm.	
May 18	++						
19		39	++	0.2 c.c. ++			
Oct. 13	++					Sal. 0.2 gm.	
Oct. 20	+	9	+	0.2 c.c. +		" 0.2 gm.	17 c.c. of 40%
Oct. 27 to							
Nov. 17						4x0.2 gm.	
Nov. 20		10	+				
1912							
Apr. 9	-	14	±	0.4 c.c. +++++		" 0.3 gm.	30 c.c. of 40%
15						" 0.3 gm.	
23	+	3	+	0.4 c.c. +++++		" 0.3 gm.	30 c.c. of 40%
30	+					" 0.3 gm.	
May 7	+	6	+	0.4 c.c. +++++		" 0.3 gm.	30 c.c. of 40%
Sept. 23	+	19	+	0.6 c.c. +++++		Neo. 0.9 gm.	
Oct. 8.	+					" 0.9 gm.	
	Chol. heart Anti.						
1913							
Jan. 31	+++	70	+	0.4 c.c. +++++	0.2 c.c. +++++	" 0.75 gm.	
Feb. 7	+++	57	±	0.4 c.c. +++++	0.4 c.c. +++++	" 0.9 gm.	30 c.c. of 40%
14	+++	28	±	0.6 c.c. +++++	0.4 c.c. +++++	" 0.9 gm.	30 c.c. of 40%
28	+++++	17	±	0.6 c.c. +++++	0.4 c.c. +++++	" 0.9 gm.	30 c.c. of 40%
Mar. 14	++	14	-	0.4 c.c. +++++	0.4 c.c. +++++	" 0.75 gm.	30 c.c. of 40%
27	+++++	7	+	1.0 c.c. +++++	0.6 c.c. +++++	" 0.75 gm.	30 c.c. of 40%
Apr. 9	+++	7	+	1.0 c.c. +	0.6 c.c. +++++	" 0.9 gm.	30 c.c. of 40%
June 3	+++++	5	±	1.0 c.c. ++	0.8 c.c. +++++	Sal. 0.5 gm.	30 c.c. of 40%
June 12	+++++					Neo. 0.9 gm.	
17	+++++	2	-	1.0 c.c. ±	1.0 c.c. +++++	Sal. 0.5 gm.	30 c.c. of 40%
July 2		4	-			" 0.5 gm.	30 c.c. of 40%
15	+++	2	-		0.8 c.c. +++++	" 0.5 gm.	30 c.c. of 40%
29	+++	1	-		1.0 c.c. ++	" 0.5 gm.	30 c.c. of 40%
Aug. 12		3	-		0.8 c.c. ++	" 0.5 gm.	30 c.c. of 40%
Sept. 9	± ±					" 0.5 gm.	
23	--	2	±	1.0 c.c. -	1.0 c.c. +++++	" 0.5 gm.	30 c.c. of 50%
Oct. 7	--	3	-	2.0 c.c. ±	2.0 c.c. +++++	Neo. 0.75 gm.	30 c.c. of 50%
21	± ±					" 0.75 gm.	
Nov. 17						Sal. 0.5 gm.	
Dec. 1	+++++					" 0.5 gm.	
22	+++++					0.6 gm.	
1914							
Jan. 19		3	-	2.0 c.c. -	2.0 c.c. ++		
27	++						
Mar. 16	++					" 0.5 gm.	
Mar. 30	+++					" 0.5 gm.	
Apr. 13	-					" 0.5 gm.	
Apr. 30	± ?					" 0.5 gm.	
May 28	-					" 0.5 gm.	
June 12	-	3	-		2.0 c.c. -		
1915							
Feb. 27	-	4	-		2.0 c.c. -		

football game, six months later lightening pains in legs appeared and have continued. Pains in chest for one year. Two years ago band-like sensation below knee. Difficulty in walking for three years. Has instructed himself in Fraenkel movements with considerable improve-

ment in walking. On admission, pupils showed only slight reaction to light; there was marked ataxic gait, marked Romberg, loss of sense of position in lower extremities, prolonged pain sensation below knees, hypoaesthesia over trunk below the second intercostal space, superficial and deep reflexes all absent. When first seen this patient presented the signs of an extensive degeneration of the cord. During the first six months, he received repeated small intravenous injections of salvarsan with some clinical improvement, but only slight alteration in the cerebrospinal fluid. This consisted in somewhat decreased pleocytosis and decreased globulin, the Wassermann reaction remaining about the same strength. During 1912, he would report only occasionally for treatment and discontinued it altogether in the last three months of that year. At the end of this period he suffered a clinical relapse consisting of partial deafness, diplopia, and marked increase in pain. The cerebrospinal fluid showed an increased pleocytosis and increased strength of the Wassermann reaction. From this time on he faithfully continued treatment, which consisted of combined intravenous and intraspinal injections given in courses of six to eight treatments followed by free intervals of four to six weeks. Although the improvement in the condition of the cerebrospinal fluid was slow under this treatment, it was continuous and after a year the only abnormality was a weak Wassermann reaction in 2 c.e. quantities. Because of persisting positive reaction in the blood, another course of salvarsan was given intravenously.

The behavior of the Wassermann reaction in the blood serum was of interest. During the first year of the disease the reaction decreased steadily. However, it was only tested with a liver antigen. With cholesterinized antigen a strongly positive reaction continued until September, 1913. Upon the resumption of salvarsan treatment in November of this year, the reaction became strong again, after a month without treatment it was weaker, but again showed a strong provocative phase after which it became completely negative and remained so. When the patient was first seen although the clinical findings indicated a very advanced tabes, the cerebrospinal fluid findings indicated an active meningitis. Under prolonged and intermittent treatment, the laboratory evidence of active disease disappeared and there was no advance in the tabetic process except possibly the development of complete Argyll-Robertson pupils. The clinical relapse in January, 1913, with a simultaneous increase in pleocytosis

and in the Wassermann reaction is worthy of special notice and shows the importance of treating this patient until the cerebrospinal fluid became normal. The addition of the intraspinal to the intravenous treatment seems to have been especially advantageous. The fact that at the end of treatment all laboratory findings were negative and have not recurred indicates a cure.

TABLE XIII

F. H. H. Age 39. Tabes Dorsalis, 4 years ? Syphilis, 12 years.

DATE	BLOOD	CEREBROSPINAL FLUID			TREATMENT	
	W. R.	Cells per c.mm.	Noguchi Glob.	Wassermann Reaction	Intravenous	Intraspinal Serum
1913						
Mar. 18	±	24	±	0.2 c.c. ++++	Sal. 0.4 gm.	30 c.c. of 40%
20	+	42	±	0.2 c.c. ++++	" 0.5 gm.	30 c.c. of 40%
Apr. 17	++	9	±	0.4 c.c. ++++	" 0.5 gm.	30 c.c. of 40%
May 13	+	2	±	0.4 c.c. ++++	" 0.5 gm.	30 c.c. of 40%
June 3	+		±	0.4 c.c. ++++	" 0.5 gm.	30 c.c. of 40%
19	+	5	+	0.4 c.c. ++++	" 0.5 gm.	30 c.c. of 40%
July 7	±	2	+	0.4 c.c. ++++	" 0.5 gm.	30 c.c. of 40%
Sept. 19	-	3	-	0.6 c.c. ++++	" 0.5 gm.	30 c.c. of 40%
Oct. 10	-	3	±	0.6 c.c. ++++	" 0.5 gm.	30 c.c. of 50%
24	-	2	±	0.4 c.c. ++++	" 0.5 gm.	30 c.c. of 50%
Nov. 21	-	2	±?	0.8 c.c. ++++	" 0.5 gm.	30 c.c. of 50%
Dec. 12	-	2		0.6 c.c. ++++	" 0.5 gm.	30 c.c. of 50%
1914						
Jan. 16	-	1	-	0.6 c.c. ++++	" 0.4 gm.	
Feb. 6	-	1	-	0.6 c.c. ++++	" 0.5 gm.	30 c.c. of 50%
27	-	2	±	0.4 c.c. ++	" 0.5 gm.	30 c.c. of 50%
Apr. 3	-	1			" 0.5 gm.	40 c.c. of 50%
May 4	-	1	±	2.0 c.c. ++++	" 0.5 gm.	40 c.c. of 50%
June 5	-	4		1.0 c.c. ++++		40 c.c. of 50%
July 10	-	4	+	2.0 c.c. ++++	" 0.5 gm.	40 c.c. of 50%
24	-	0	-	2.0 c.c. ++++	" 0.5 gm.	40 c.c. of 50%
Aug. 7	-	1	±?	2.0 c.c. ++++	" 0.5 gm.	40 c.c. of 50%
Sept. 4	-	2	-	2.0 c.c. ++++	" 0.5 gm.	40 c.c. of 50%
1915						
June 17	-	2	-	2.0 c.c. -		

While the discontinuing of treatment may at times be followed by an increase in the abnormal elements in the cerebrospinal fluid, the contrary is not infrequently seen. This leads us to speak of the importance of giving treatment in courses with periods of rest and of determining what has occurred during these free intervals. Case 13 (F. H. H.) illustrates this point. Twelve years before admission, he had a chancre followed by a rash. He took KI and pills for two and one-half years and inunctions for two months, then four injections of mercury yearly for six years. Four years ago began to tire easily and had dull pains shooting up and down the spine. Six months later he developed weakness in legs and difficulty in walking. He then re-

ceived thirty-seven injections of mercury with relief from pain. Two years ago had slight numbness in arms and legs. In January, 1911, two injections of salvarsan; July, 1912, lumbar puncture—66 cells, globulin increased, Wassermann reaction strongly positive, amount not given. September 16 to October 7, 1912, neosalvarsan. Inunctions of mercury for the past month. Condition on admission: Irregular pupils, reaction slowly to light; sensation normal; absence of tendo Achilles and patellar reflexes; no mental disturbance. Because of the markedly abnormal condition of the cerebrospinal fluid, even though the patient was under the influence of fairly active treatment, it was considered advisable to give combined intraspinal and intravenous injections immediately. There was a prompt diminution in pleocytosis and a steady weakening of the Wassermann reaction. When treatment was intermitted in July, 1913, the fluid continued to show improvement. Slight increase in the intensity of the Wassermann reaction occurred when the treatment was resumed. Treatment was again intermitted in February, 1914, the Wassermann reaction became much weaker and remained of practically the same strength under irregular treatment until September. Treatment was then stopped and a year later the cerebrospinal fluid was normal. There has been no advance in the clinical symptoms. As the patient lives in a distant city, we have been unable to examine the fluid lately.

#### GROUP IV.—PARALYTIC DEMENTIA

When compared with the rate of diminution of the abnormal elements in the spinal fluid and the arrest of clinical symptoms and signs in tabes, the treatment of paresis has been a distinct disappointment. When compared with the results of our therapeutic efforts in the presalvarsan era, however, treatment is encouraging and distinctly worth while. The results reported by different observers vary widely. These differences are no doubt explainable in the class of patients who come under observation and treatment. As might be expected in a disease which involves the parenchymatous tissue so extensively, the earlier the treatment is instituted, the better the chance of improvement. If, on the other hand, the condition has progressed to such an extent that it is necessary to commit the patient to an institution, the chances for improvement are diminished. The increasing difficulty in favorably influencing the disease as it grows older is illustrated in Case 14.



TABLE XIV

R. P. Age 43. Tabo-paresis.

DATE	BLOOD	CEREBROSPINAL FLUID				TREATMENT	
	W. R.	Cells	Glob.	Wassermann Reaction	Gold	Salvarsan	Intraspinal Serum
1913							
Apr. 7	++++	47	++	0.4 c.c. +++++		0.4 gm.	30 c.c. - 40%
22	++++	7	+	0.6 c.c. +++++		0.5 gm.	30 c.c. - 40%
May 6	++++	11	+	0.8 c.c. +++++		0.5 gm.	30 c.c. - 40%
20	++++	13	±	0.6 c.c. +++++		0.5 gm.	30 c.c. - 40%
June 3	++++	9	+	0.6 c.c. +++++		0.5 gm.	30 c.c. - 40%
20	++++	14	+	1.0 c.c. +++++		0.5 gm.	30 c.c. - 40%
1914							
Jan. 16	++++	3	±	0.6 c.c. +++++		0.5 gm.	
23	++++	4	±	0.6 c.c. +++++		0.5 gm.	40 c.c. - 50%
Feb. 5	++++	6	±			0.5 gm.	40 c.c. - 50%
23	++++	6	±	0.8 c.c. +++++		0.5 gm.	34 c.c. - 50%
Mar. 10	++++	6	±	0.6 c.c. +++++		0.6 gm.	40 c.c. - 50%
23	++++	5	±	0.8 c.c. +++++		0.5 gm.	40 c.c. - 50%
Apr. 6	++++	3	-	1.0 c.c. +++++		0.5 gm.	40 c.c. - 50%
20	++++					0.5 gm.	
27	++++					0.5 gm.	
1915							
Dec. 11	++++	16	+	0.6 c.c. +++++		0.4 gm.	14 c.c. - 100%
20	++++	42	+	0.6 c.c. +++++		0.3 gm.	
30	++++		+	0.6 c.c. +++++		0.4 gm.	15 c.c. - 100%
1916							
Jan. 7	++++	8	±	0.2 c.c. +++++		0.4 gm.	15 c.c. - 100%
29	++++	5	±	0.2 c.c. +++++		0.5 gm.	15 c.c. - 100%
Feb. 12	++++	2	±	0.6 c.c. +++++		0.5 gm.	15 c.c. - 100%
25	++++	5	±	0.6 c.c. +++++		0.5 gm.	14 c.c. - 100%
Mar. 11	++++	9	±	0.6 c.c. +++++		0.3 gm.	15 c.c. - 100%
25	++++	10	±	0.6 c.c. +++++		0.3 gm.	15 c.c. - 100%
Apr. 7	++++	9	±	0.6 c.c. +++++		0.35 gm.	15 c.c. - 100%
May 6	++++	4	+	0.6 c.c. +++++		0.4 gm.	15 c.c. - 100%

Case 14 (R. P.). He was first seen March 31, 1913. Denied primary or secondary syphilitic lesion. In 1903 he had a sore throat which was suspected of being syphilitic in nature. Has had stiffness in arms and legs for ten years. Has had tremor of the hands for four years, and shooting pains in various parts of the body. Four months ago following a fall he had weakness of the muscles of the left leg and foot. This gradually improved. Patient feels that his mental acuity is diminishing and his memory is poor especially for names of people. He is much worried over business affairs. His physical examination showed small pupils reacting with only slight excursion to light. Coarse tremor of tongue, arms and legs, slight incoordination in legs. No sensory disturbances. All tendon reflexes are overactive except the tendo Achilles which are absent. Mentally, patient was nervous and depressed, but well oriented. The first course of treatment which was given in a fairly early period in the disease, resulted in a rapid diminution of both pleocytosis and globulin, and in the strength of the Wassermann reaction. He then

discontinued treatment, but six months later was persuaded to return for another course. At this time there was no increase in cells, but the Wassermann reaction was stronger. Again, as in the first course, treatment favorably influenced the laboratory findings, and again the patient discontinued his treatment voluntarily. He was, however, able to resume his work in a very responsible position. In the fall of 1915, he suffered a sudden attack of mental depression and for a time had to be confined in an institution. Treatment which was again resumed at this time had practically no effect on the strength of the Wassermann reaction in the spinal fluid. Several gold tests at this time showed constantly the paretic type. Patient has again refused to be treated and while on superficial examination he appears fairly normal, still his mental condition is such that he can not return to his former work.

The diminishing influence of treatment as the disease progresses is still more strikingly brought out in Case 15 (G. W. C.). On admission, July, 1913, he complained of difficulty in thinking and of aching sensation in the leg which had started seven months previously. A diagnosis of neurasthenia had been made. He was occasionally at loss for a word. The examination showed unequal, dilated pupils, right reacted only slightly to light, left not at all; diminished hearing, no Romberg, no incoordination, sensations normal, deep reflexes sluggish. When patient was admitted provisional diagnosis was paresis, but the symptoms were mainly neurasthenic in character; the later symptoms, however, confirmed the original diagnosis. During the first course of treatment, there was a rapid diminution in pleocytosis, and in the Wassermann reaction in the spinal fluid, so that after four months it required 2 c.c. of fluid to give a positive reaction. After patient had been under treatment for nine months, he discontinued it for three months. At the end of this interval, there was a definite clinical relapse, patient showing distinct mental exaltation. The Wassermann reaction in the blood had become strongly positive; the spinal fluid showed 77 cells and a positive Wassermann reaction. After two months' treatment there was again a definite drop in the cell count but not so marked as with the first course. The Wassermann reaction responded more slowly. Again patient discontinued treatment. After an interval he returned with a relapse to 90 cells in the fluid, the Wassermann reaction remained of the same strength. After nine treatments the cells dropped to 10, the globulin remained

TABLE XV

G. W. C. Age 44. Paresis. Syphilis, Duration?

DATE	BLOOD	CEREBROSPINAL FLUID			TREATMENT	
	W. R.	Cells	Noguchi Glob.	Wassermann Reaction	Intravenous	Intraspinal Serum
1913						
July 17	++++	34	+	0.6 c.c. +++++	Sal. 0.5 gm.	
22	++++				" 0.4 gm.	30 c.c. of 40%
29	+++	30	++	0.8 c.c. ++++	" 0.5 gm.	
Aug. 10	++++				" 0.5 gm.	
18	+++				" 0.5 gm.	
26	+++				Neo. 0.9 gm.	30 c.c. of 50%
Sept. 17	+++	5		1.0 c.c. -	" 0.9 gm.	30 c.c. of 50%
Oct. 1	++++	7	+	2.0 c.c. ++++	" 0.5 gm.	30 c.c. of 66%
Nov. 13	++++	8	+	2.0 c.c. ++	" 0.1 gm.	
Nov. 28	++++					
Dec. 5 to						
Mar. 27/14					Sal. 9x0.5 gm.	
June 29	++++	77	+	0.6 c.c. +++++	" 0.5 gm.	
July 1	++++	65	+	0.6 c.c. +++++	" 0.5 gm.	40 c.c. of 50%
20	+++	57	+	0.6 c.c. +++++	" 0.5 gm.	35 c.c. of 50%
Aug. 3	++	22	+	2.0 c.c. +++++	" 0.5 gm.	40 c.c. of 50%
10	+++				" 0.5 gm.	
20	+++	22	+	2.0 c.c. +++++	" 0.5 gm.	40 c.c. of 50%
Sept. 4	++	15	+	0.8 c.c. +++++	" 0.5 gm.	40 c.c. of 50%
Nov. 23	++++	90	+	0.8 c.c. +++++	" 0.5 gm.	40 c.c. of 50%
Dec. 7	++	36	+	0.8 c.c. +++++	" 0.5 gm.	40 c.c. of 50%
21	++	14	+	0.6 c.c. +++++	" 0.5 gm.	40 c.c. of 50%
1915						
Jan. 19	++	20	+	0.6 c.c. +++++	" 0.5 gm.	35 c.c. of 50%
Feb. 15		32	+	0.6 c.c. +++++	" 0.5 gm.	40 c.c. of 50%
Mar. 1	++	12	+	0.6 c.c. +++++	" 0.5 gm.	40 c.c. of 50%
15	++++	13	+	0.6 c.c. +++++	" 0.5 gm.	40 c.c. of 50%
27		12	+	0.8 c.c. +++++	" 0.5 gm.	40 c.c. of 50%
Apr. 12	++	10	+	0.6 c.c. +++++	" 0.5 gm.	40 c.c. of 50%
July 20		73	++	0.8 c.c. +++++	" 0.5 gm.	40 c.c. of 50%
Aug. 6		20	++		" 0.5 gm.	40 c.c. of 50%
18		20			" 0.5 gm.	40 c.c. of 50%
Sept. 9	+	28		1 c.c. +++++	" 0.5 gm.	
23		11		0.4 c.c. +++++	" 0.5 gm.	40 c.c. of 50%
Oct. 11		20			" 0.5 gm.	40 c.c. of 50%
Nov. 9	+	25	±	0.6 c.c. +++++	" 0.5 gm.	40 c.c. of 50%
22	++++	17		0.6 c.c. +++++	" 0.5 gm.	40 c.c. of 50%
Dec. 6	++	15	+	0.8 c.c. +++++	" 0.5 gm.	40 c.c. of 50%
22	±	16	+	0.8 c.c. +++++	" 0.5 gm.	40 c.c. of 50%
1916						
Jan. 1					" 0.5 gm.	
13					Neo. 0.6 gm.	
Feb. 2		20			Sal. 0.5 gm.	40 c.c. of 50%
18		17			" 0.5 gm.	40 c.c. of 50%
Mar. 3		7		0.6 c.c. +++++	" 0.5 gm.	40 c.c. of 50%
Apr. 8				0.6 c.c. +++++	" 0.5 gm.	40 c.c. of 50%
21	++++			0.6 c.c. +++++	" 0.5 gm.	40 c.c. of 50%
May 6					" 0.5 gm.	40 c.c. of 50%
June 28	++++	20		0.6 c.c. +++++	" 0.5 gm.	40 c.c. of 50%

unchanged, and the Wassermann reaction showed no decrease in intensity. However, the patient was somewhat improved clinically. After another interval of three months without treatment another clinical relapse occurred as shown by speech disturbance, slightly diminished capacity for work and definite euphoria. At this time there were 73 cells, globulin reaction stronger, the Wassermann reaction the same intensity. After July, 1915, the treatment was given once or

twice every month, but in spite of this there was a progressive downward course in the clinical condition and the cerebrospinal fluid was practically uninfluenced. There were increasing speech disturbance, increased difficulties in writing, weakness in the right leg, occasional feeling of numbness and pricking in the forearm and right leg. Patient attempted to continue his business, but was less capable than formerly. It was never thought necessary to commit him to an institution, and he died August, 1916 while on a business trip. The gold curves during the last year of his life were all of strongly paretic type.

These two cases are fairly typical of what may be expected in the treatment of paresis. First, marked clinical improvement to the extent of complete remission with simultaneous improvement in the condition of the cerebrospinal fluid. Second, marked or complete remission with practically no improvement in the condition of the cerebrospinal fluid. Third, a stationary condition of the cerebrospinal fluid and a progressive downward course clinically, even though most intensive treatment is being applied. In no case can we accurately prognosticate as to which of these three types of response will occur. Most of the patients, late in the disease, show the tendency to a progressive downward course even under treatment.

What then is the effect of treatment in paresis? In the majority of patients who are treated at an early period in the disease, there is an increased number of remissions. As a consequence of this, there are longer periods of usefulness, and shorter periods of confinement in institutions. Several observers have stated that where formerly many of the paretics in the insane asylums were bedridden for long periods, now they are helpless for a much shorter time, and the patients are often socially possible until near the time of death.

PATIENTS CLINICALLY NOT PARALYTICA DEMENTIA IN WHOM THE  
CEREBROSPINAL FLUID SHOWS PARETIC TYPE OF GOLD CURVE

With the application of the colloidal gold test to the cerebrospinal fluid of all patients with cerebrospinal involvement, we are occasionally finding a paretic type of gold curve in all stages of the disease; at least in all intervals after infection. During the past year we have had one patient who within less than a year from the time of his initial lesion, showed pronounced changes in the cerebrospinal fluid with a marked paretic type of gold curve. Patients with apparently

an exudative lesion, such as Case 5, also have given this type of curve in their cerebrospinal fluids, but more frequently the paretic curve is found in the fluids of patients with clinical signs and symptoms of tabes dorsalis. The question naturally arises as to what influence the conditions which give rise to this peculiar type of gold curve may have upon the response to treatment. We have seen that when patients with early paresis give this type of curve that the influence of treatment may be slight and that the curve may be unaffected. On the other hand, a case like Case 5 with exudative lesions may show a rapid reversal of the paretic curve to a luetic curve.

TABLE XVI

F. C. Male. Age 52. Tabo-paresis? Syphilis, 14 years.  
Lancinating pains, 2 years.

DATE	BLOOD		CEREBROSPINAL FLUID			TREATMENT		REACTION
	W. R.	Cells	Glob.	W. R. c.c.	Gold	Intrav. Sal. gm.	Intrasp. Serum 100%	
1915								
Apr. 5	++++	20	++	0.6 + + + +	55554 00000	0.3		
19	++++		++			0.3		
May 3	++++	6	++			0.4	15 c.c.	
17		30	++	0.6 + + + +		0.35	15 c.c.	
June 5	++++	8	++			0.4	15 c.c.	
20	++++	2	++	0.6 + + + +		0.4	15 c.c.	
Aug. 8		6	++	0.6 + + + +		0.4	13 c.c.	Vomiting, headache, chill 6 hrs. p. IV
Dec. 5	++++	10	++	1.0 + + +		0.4	17 c.c.	
1916								
Jan. 15	++++	13	++	1.0 + + + +		0.35	16 c.c.	Nausea, fullness in head
Feb. 12	++++	11	++	2.0 + + + +		0.25	15 c.c.	Urticaria following IV
26	++++	8	+	2.0 + + + +		0.3	15 c.c.	" " "
Mar. 18	++++	6	±	2.0 + +		0.3	15 c.c.	Flushing, choking
Apr. 8	++++	6	+	2.0 + + + +		0.4	15 c.c.	" " urticaria
22	++++	20	+	2.0 + + + +		0.3	15 c.c.	" " "
May 20	++	9	++	2.0 -	11221 00000	0.3	15 c.c.	Urticaria only reaction
June 3	++++	20	++			0.3	15 c.c.	" " "
17	++++			2.0 + +		0.3	15 c.c.	" " "
July to	Oct.					Hg. Sal. hypo		KI
Nov. 4	±	12	+	2.0 +	11111 00000			
25	±					0.2		Urticaria
Dec. 9	+					0.2		Flushing, choking
1917								
Jan. 6	+++					0.3		Urticaria
20	±	28	+	0.6 + + + +	11233 21000			

The response of a tabetic with a paretic gold curve in his fluid to intensive treatment is illustrated in Case 16 (F. C.) who was admitted April 3, 1915. Infection fourteen years ago with rash. Treatment consisted of pills for one year, inunctions one month. Two years ago

hot flashes down arms and legs recurring over periods of two or three days. Six months ago shooting pains in right leg, improvement after massage. Numbness in soles of feet for several months. Ten days ago return of the pain. For two years cold baths have caused him pain where formerly they were enjoyed. Examination showed Argyll-Robertson pupils, diminished hearing, hyperalgesia over front of chest, band of hyperesthesia to cold over lower trunk, pain sensation delayed over legs and lower trunk, deep sensations all retained, slight Romberg, no ataxia, arm reflexes exaggerated, knee jerks normal, ankle jerks much diminished. The first course of treatment was accompanied by a satisfactory diminution in pleocytosis, but there was no effect on the intensity of the Wassermann reaction in the fluid. After discontinuing treatment for four months, the fluid Wassermann reaction was weaker. This is contrary to what is usually found in paresis. Upon resuming treatment, the reaction in the fluid rapidly diminished but the cells showed a tendency to remain above normal in number. The patient has shown marked anaphylactic symptoms during intravenous injections followed by urticaria and dermatitis. During a course of mercury and iodide, the condition of the fluid remained the same except that the gold curve became weaker. Because of only the slight abnormality of the cerebrospinal fluid it was felt that resumption of intravenous treatment alone might be sufficient. The patient, however, has continued to exhibit marked hypersensitiveness to the salvarsan and after three injections has shown an increased pleocytosis, a stronger Wassermann reaction, and a more marked luetic type of gold curve in his fluid. He has, however, shown marked subjective improvement, but practically no change in the physical signs. The difficulty in maintaining the improvement in the cerebrospinal fluid and the original parietic type of gold curve suggests that this patient may follow a course similar to that illustrated in the two cases of paresis. Whether the active syphilis can be permanently eliminated only the future will answer.

The rapid rate at which the gold curve may be reversed and the other abnormal elements in the spinal fluid diminished is illustrated by Case 17 (B. J.) who was admitted August 30, 1916. He had gonorrhea twelve years ago, no history of primary or secondary syphilitic lesions. For past eight years attacks of epigastric pains, sharp in character, aggravated by eating, relieved by vomiting. For the past two months, vomiting and pain much worse, suprapubic pain

TABLE XVII

B. J. Male. Painter. Age 36. Tabes. Gastric Crises, 8 years.  
Syphilis?

DATE	BLOOD	CEREBROSPINAL FLUID				TREATMENT			
	W. R.	Cells	Glob.	Wassermann Reaction	Gold	Intrav. Sal.	Intrasp. Serum	KI gm.	Hg.
1916 Sept. 2	0	21	+	0.6 c.c. ++++	55554 21000			50	HgCl <sub>2</sub> 8 $\frac{1}{8}$ gr. hypo.
" 2-21 " 21		32	++	2.0 c.c. ++++	55554 42100		15 c.c. 100%		
Oct. 3	0	57	++	2.0 c.c. ++++		0.2 gm.	15 c.c.	"	
11	0	21	++	1.0 c.c. ++++		0.35	12 c.c.	"	
17	0	13	++	2.0 c.c. +		0.3	12 c.c.	"	
26	0	15	++	2.0 c.c. +		0.2	15 c.c.	"	
Nov. 3	0	17	-	2.0 c.c. ++		0.3	12 c.c.	"	
16	0	11				0.3	15 c.c.	"	
Dec. 13	0	8	+	2.0 c.c. -	22232 10000	0.3	12 c.c.	"	
" 28	0	4	+	2.0 c.c. +++		0.35	15 c.c.	"	
1917 Jan. 11	0	8	+	2.0 c.c. +		0.3	15 c.c.	"	
24	0	0		2.0 c.c. $\pm$	11221 10000	0.25	15 c.c.	"	

during voiding, occasional incontinence of urine. Examination showed an emaciated man, vomiting almost constantly, bladder markedly distended and inflamed, pupils react sluggishly to light, reflexes normal, only disturbance in sensation are two small areas of hyposthesia over midscapula, and two areas of hyperalgesia over anterior chest just external to nipples, and a small patch over left side of epigastrium. After treatment was started the vomiting diminished somewhat, but the attacks would occur two or three times a week. He remained in the hospital until November 4, with slow but steady improvement. Occasional attacks of vomiting. After leaving hospital vomiting became less frequent. There was marked constipation, occasional vomiting while straining at stool. The improvement in the condition of the cerebrospinal fluid has been steady in all respects with a reversal in the type of the gold curve to a luetic type which is also diminishing in strength. The intraspinal treatments were combined with intravenous treatments from the beginning because we felt that the parietic type of gold curve made the prognosis more grave. In fact, because of the constant association of parietic type of curve in paresis we feel that when this condition is present in the fluid of patients in whom other forms of cerebrospinal syphilis are thought to be present, the most intensive treatment should be applied from the beginning, and that our prognosis as to ultimate perma-

ment arrest should be guarded. The exact influence of this condition in the cerebrospinal fluid is still a matter for investigation.

#### SUMMARY

In this presentation the various factors considered in classifying the cases are: time since infection, clinical picture, laboratory findings, and response to treatment. The following groups are recognized:

##### 1. Early Meningitis.

(a) Cases which respond readily to the general administration of salvarsan and mercury.

(b) Cases which respond more slowly to salvarsan intravenously, and tend to relapse when salvarsan is discontinued, or mercury is substituted.

(c) Cases which do not clear up under most intensive general treatment, but which respond satisfactorily to intraspinal treatment.

2. Later forms of central nervous syphilis of the exudative type. The abnormal elements in the cerebrospinal fluid usually disappear rapidly under general administration of iodides, mercury and salvarsan.

##### 3. Tabes Dorsalis.

(a) Cases which show a rapid response to general treatment.

(b) Cases which show no improvement or very slow improvement under general treatment.

(c) Cases which show a satisfactory response to intraspinal treatment alone.

(d) Cases which have responded slowly to general treatment, but which respond more rapidly when intraspinal injections of "auto-salvarsanized serum" are given.

(e) Cases which relapse when treatment is discontinued.

(f) Cases which continue to improve when treatment is discontinued.

##### 4. Paralytica Dementia.

(a) Cases with marked improvement in both clinical signs and the condition of the cerebrospinal fluid.

(b) Cases with marked clinical improvement but no change in the cerebrospinal fluid.



(c) Cases with progressive downward clinical course and stationary condition of the cerebrospinal fluid.

5. Patients clinically not paralytica dementia in whom the cerebrospinal fluid shows a paretic type of gold curve.

(a) Cases which respond rapidly to combined intravenous and intraspinal treatment.

(b) Cases which respond more slowly and show a decided tendency for the abnormal elements to recur when treatment is discontinued.

#### CONCLUSION

Before undertaking the treatment of a patient with any form of cerebrospinal syphilis, it is important to determine what symptoms are due to inflammation or exudation and what are due to degeneration of tracts or cortex. It is also advisable to determine the intensity of the irritative condition as indicated by the cerebrospinal fluid. In general the lesions due to inflammation or exudation are much improved or eliminated by the general treatment of the patient. Those due to degeneration are little, if any, affected. Treatment should be directed not only towards the elimination of symptoms, but towards the elimination of the underlying process, namely, syphilis. In most patients with early meningitis and in those with what was formerly termed tertiary syphilis of the central nervous system, the symptoms due to exudation respond in a satisfactory manner to the general administration of salvarsan, mercury, and potassium iodide. Occasionally, a case is met in which intraspinal treatment seems to be necessary in order to eradicate completely the central nervous lesions. Likewise in tabes dorsalis, many cases respond satisfactorily to the general administration of salvarsan and mercury. On the other hand, in a considerable number of tabetics, the addition of intraspinal injections of serum to intravenous treatment with salvarsan seems to hasten the elimination of abnormal elements in the cerebrospinal fluid and lead to a permanent arrest of the degeneration. It is advisable to continue the treatment of patients suffering from cerebrospinal syphilis or tabes dorsalis until the cerebrospinal fluid is normal and remains so. A possible exception may be made in reference to excess globulin, for an increased globulin is not infrequently found years after all other abnormal elements have disappeared from the fluid.

In paralytica dementia, while much benefit may be expected in

increasing the number and length of remissions, the ultimate hope for recovery is slight. When a paretic type of gold curve is found in the fluid of patients in whom the clinical diagnosis of paresis is not justified, the most intensive form of treatment should be instituted from the beginning. It is probable that the finding of this paretic type of gold curve often helps us to make a diagnosis of paresis before clinical symptoms of the disease are present. This early diagnosis with consequent early treatment may be of extreme importance in preventing the development of the outspoken condition. Finally, treatment must be individualized, given in courses, and the condition of the fluid determined at the end of each course and at the beginning of the subsequent course. In this way, the indication for kind of treatment, as well as the manner of response, is much more certainly determined than if we depend on clinical symptoms and objective findings alone.

## COMPLEMENT FIXATION IN SYPHILIS\*

WITH A PRELIMINARY REPORT OF A NEW TECHNIC

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### INTRODUCTION

SINCE the epoch-making announcement of the utilization of the principle of complement fixation in the diagnosis of syphilis by Wassermann<sup>1</sup> and his associates, many attempts to simplify and render more accurate the original technic have been made. In fact, so many modifications have been announced that some one has remarked that every serologist has his own method, and as Vedder<sup>2</sup> has so well said, "One is impressed by the fact that the Wassermann reaction must be a test of most surprising merit to have survived all the clumsy technic that has been perpetrated in its name."

Five factors enter into the test in all methods, although the sources of these factors vary greatly. Three of these factors compose the so-called hemolytic system and are complement, erythrocytes and hemolytic amboceptor, corresponding to the erythrocytes used. The other two factors are the patient's serum and antigen.

### WASSERMANN'S ORIGINAL METHOD

In the original Wassermann<sup>1</sup> technic the sheep hemolytic system is employed. That is, the erythrocytes used are thoroughly washed cells of the sheep made up to 5 per cent dilution, and the amboceptor is the blood serum of a rabbit immunized against sheep's corpuscles. The complement is supplied by fresh guinea pig serum. The patient's serum is inactivated at 55° C. for one-half hour to destroy the native complement, and the original antigen was an aqueous extract of syphilitic fetal liver. This latter was used because of the fact that such liver contains many *Treponemata pallida*, and Wassermann considered that the reaction was of a true antigen-antibody nature between the extract of the spirochetes and the syphilitic antibodies of the patient's serum.

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Before the actual performance of the test the amboceptor is titrated to determine its strength. Aseptic technic is enjoined. A series of test tubes is prepared by placing in each 1 c.c. of a 1:10 dilution of fresh guinea pig serum (0.1 c.c. pure serum), 1 c.c. of a 5 per cent solution of washed sheep's cells, increasing amounts of antishoop amboceptor serum, and making the whole amount up to 5 c.c. with normal salt solution. The tubes are incubated at 37° C. for two hours, when the tube containing the smallest amount of amboceptor which shows complete hemolysis is determined and this amount of amboceptor considered as one *unit*.

The aqueous extract of syphilitic fetal liver, or antigen, must also be first titrated to determine the smallest amount which of itself will inhibit hemolysis, that is, its *anticomplementary* dose. This is determined by adding to a series of test tubes increasing amounts of the extract, 1 c.c. of complement, 2 units of amboceptor, and 1 c.c. of corpuscle suspension and the whole made up to 5 c.c. The tubes are incubated for two hours at 37° C. and only such extracts are used which in a dose of 0.4 c.c. do not interfere with hemolysis. It must also be determined that in considerably larger doses (0.8 c.c.) the extract of itself will not hemolyze the dose of corpuscles.

Three tubes are used for each serum tested, three each for the positive and negative control sera, and three tubes for control of the hemolytic system.

Into the first tube of each serum, including the positive and negative sera, is placed 1 c.c. of a 1 to 5 dilution of antigen and into the second, 0.5 c.c.; the third tube receives no antigen. The first and third tubes receive 0.2 c.c. of inactivated serum and the second 0.1 c.c. Each tube, including the first two of the hemolytic system control tube, receives 1 c.c. of the diluted guinea pig serum, and the total amount is made up to 3 c.c. The tubes are now incubated for one hour at 37° C., after which 2 units of amboceptor, diluted so that each cubic centimeter contains two units, and 1 c.c. of the corpuscle suspension are added to each tube, except the last two tubes of the hemolytic system control, to each of which are added 1 c.c. of salt solution and 1 c.c. of corpuscle suspension. The incubation is now continued for two hours, when the tubes are placed in the ice box overnight. The following morning the results are read as follows: If tubes 1 and 2 of a serum show complete inhibition of hemolysis, the corpuscles have settled to the bottom, and the fluid

above being perfectly clear and free of color, the reaction is strongly positive and designated + + + +. If Tube 1 shows complete inhibition and Tube 2 faint hemolysis, the reaction is designated + + +. If Tube 1 shows complete inhibition of hemolysis and Tube 2 complete hemolysis, ++ is recorded; while if Tube 1 shows partial hemolysis and Tube 2 shows complete hemolysis, the reaction is faintly positive and marked +. If Tube 1 shows doubtful binding of complement and Tube 2 shows complete hemolysis, the reaction is doubtful and designated  $\pm$ . Complete hemolysis in both Tubes 1 and 2 constitutes a negative reaction and is recorded -.

Both Tubes 1 and 2 of the negative control should show complete hemolysis, and 1 and 2 of the positive control complete inhibition of hemolysis.

Tube 3 of all sera should show complete hemolysis as no antigen is placed in these tubes. Tube 1 of the hemolytic system control tubes should show complete hemolysis and Tube 2 and 3 complete inhibition.

#### ANTIGENS

As stated above, the original Wassermann antigen was an aqueous extract of the liver of a congenitally syphilitic fetus, and is prepared as follows: The liver is weighed and cut into small pieces. To this is added four times its weight of 0.5 per cent phenol solution in normal saline. The mixture is placed in a brown bottle and shaken with a shaking apparatus for twenty-four hours. Following this it is centrifugalized until the larger pieces of liver settle to the bottom of the tubes, leaving the supernatant fluid slightly turbid. The latter is poured off into a brown bottle and placed in the ice box where, after a few days of sedimentation, it assumes a yellowish brown color and is ready for use. It should be kept in the ice box, and when it is to be used, only a sufficient quantity is carefully poured off without disturbing the sediment.

This was found by most investigators to be very unstable, although Citron<sup>3</sup> thinks this due to carelessness in handling. However, as congenitally syphilitic livers are comparatively difficult to procure, it was soon evident that in order to make the test practical, some other methods of preparing antigen must be found.

Michaelis<sup>4</sup> preserved syphilitic fetal liver in the frozen state, while Marie and Levaditi,<sup>5</sup> after pulverizing it, dried it *in vacuo* to pre-

serve it. It was not long, however, before several investigators reported that the alcoholic extracts of syphilitic fetal liver were much more stable than the aqueous extracts, and that their antigen properties were equally as good. These extracts are prepared by mincing finely a syphilitic fetal liver, then adding to it absolute alcohol in the proportion of 10 c.c. of alcohol to each gram of tissue. The mixture may be shaken in a shaking apparatus for twenty-four hours and then placed in an incubator at 37° C. and allowed to remain for ten days. Or, if a shaking machine is not available, it may be placed in the incubator at once, in which case it should be allowed to remain a few days longer. The containing vessel should be tightly stoppered to prevent evaporation. After having remained in the incubator a sufficient length of time it is filtered through a fat-free paper, or one washed with ether or alcohol, which removes any hemolytic substance which may be present. The filtrate, which is the antigen, is collected and stored in a tightly stoppered bottle in the ice box. The sediment which forms after the antigen has stood for a few days should not be removed or disturbed.

The next step in advance in the preparation of antigens for the syphilitic complement fixation test was the announcement of the fact by several investigators that extracts of normal organs would bind complement with syphilitic sera. The most significant work of the time was that of Landsteiner, Müller and Potzl,<sup>6</sup> who showed that with alcoholic extract of guinea pig heart results are obtained equal to those obtained with the extracts of syphilitic fetal liver.

The process of preparing alcoholic extracts from normal organs is the same as that described for preparing alcoholic extracts of syphilitic fetal liver. Care should be exercised in preparing these extracts that no fat is included in the mixture.

The next important antigen to be prepared was the acetone insoluble lipoid of Noguchi and Bronfenbrenner.<sup>7</sup> This antigen is prepared as follows: The heart, liver, or kidney of a man, beef, guinea pig, rabbit, or dog is finely minced and mixed with 10 parts of absolute alcohol\* and extracted for several days at 37° C. After filtration through paper the filtrate is evaporated to dryness by the use of an electric fan. The residue is taken up with a sufficient quantity of ether and placed in a tightly stoppered receptacle and kept overnight in a cool place. The turbidity will now be seen to have cleared

\*I have prepared excellent antigen with 95 per cent alcohol.

up by the settling of the insoluble particles to the bottom. The clear supernatant fluid is carefully decanted off, and placed in a clean beaker. I have found it most convenient to place the ethereal solution in a separatory funnel, as, after the insoluble particles have settled to the bottom, they may be drawn off by opening the stop-cock, leaving the clear solution. The latter is now condensed to a small quantity by evaporating off the ether, after which the concentrated solution is mixed with ten volumes of pure acetone. A light brownish precipitate is formed, which soon settles to the bottom of the vessel. After decantation of the supernatant fluid the precipitate becomes a sticky mass, which may be stored in this form, or it may be dissolved in ether in the proportion of 0.3 gram to 1 c.c. and mixed with nine volumes of pure methyl alcohol. This is the antigen and should be stored in a tightly stoppered bottle in a cool place.

In 1911 Sachs<sup>8</sup> proposed to reinforce the alcoholic extracts of normal organs with cholesterin. McIntosh and Fildes<sup>9</sup> employed this antigen and reported very favorably upon its use. The work of Walker and Swift,<sup>10</sup> which was very comprehensive, showed conclusively the value of cholesterinized antigens, especially the reinforced human heart extracts, and soon a number of investigators<sup>11</sup> reported series of cases in which it had been used with great satisfaction. It was found to be more sensitive than any antigen yet produced, giving more positive results in known specific cases, and by most investigators found not to give positive results in known negative cases.

Thomas and Ivy,<sup>12</sup> however, decried the use of cholesterinized antigens, claiming that many positive results were obtained by them in nonsyphilitic cases. Their observations have not been confirmed, except that perhaps an occasional slightly positive reaction may be obtained, upon which with any antigen, and in the absence of clinical symptoms, no one would make a positive diagnosis of syphilis.

In preparing cholesterin reinforced antigens the usual procedure is to make an alcoholic extract of normal organ (human heart is best) which is kept as a stock solution in the ice box, and to prepare a small quantity of the antigen (50-100 c.c.) by adding 0.4 per cent pure cholesterin. The latter is not readily soluble in alcohol, so the mixture should be permitted to stand at room temperature with frequent shaking for about one week before use.

Since the brilliant work of Noguchi<sup>13</sup> in cultivating the *Treppo-*

*nema pallidum*, several investigators have employed extracts of cultures of these organisms as antigen, hoping to make of the complement fixation test for syphilis a true antigen-antibody reaction.

Noguchi<sup>14</sup> prepared an aqueous extract as follows: Several strains of *treponemata* should be used and tubes containing good growths, cultivated after the method described by Noguchi, are selected. The oil is poured off, the tube filtered and broken just above the tissue, and the agar column removed. The upper or uninfected portion is cut off and discarded, and the remainder is ground by shaking with marbles and a sufficient quantity of normal salt solution in a sealable porcelain jar in a shaking apparatus until the *treponemata* are disintegrated. The emulsion is transferred to a sterile bottle, heated to 60° C. for thirty minutes and 0.4 per cent phenol added.

Alcoholic extracts were prepared by Craig and Nichols<sup>15</sup> by mixing the *treponemata* containing agar with ten times its weight of absolute alcohol and extracting for ten days with frequent shaking. Following the extraction the mixture is filtered and the filtrate evaporated to one-third its volume.

Noguchi found that the aqueous extracts gave a positive reaction in certain cases of treated syphilis, or in those in which the infection had existed for a long time without symptoms when the lipoidal antigen was negative or faintly positive. He thinks that the value of the pallidum extracts is a "gauge for the defensive activity of the infected host."

Craig and Nichols, using their alcoholic extracts of *Treponema pallidum*, found 17 sera gave the same results as the alcoholic extracts of syphilitic liver, 4 gave weaker reactions, 6 stronger, and 4 gave positive reactions where the liver antigen gave negative reactions. But of 20 sera which gave positive reactions with the liver antigen, 7 gave negative reactions with the pallidum antigen.

These investigators also showed that positive reactions could be obtained in syphilitics with antigens prepared from cultures of *Spirocheta pertenuis* and *Spirocheta microdentia*, although usually weaker than those obtained with the *Treponemata pallidum* antigen.

#### HEMOLYTIC SYSTEMS

In the early days of the complement fixation test for syphilis, it was not long before it was pointed out by several different observers that all human sera contain variable amounts of natural antisheep



hemolytic amboceptor, and that sometimes, at least, it is present in sufficient quantity to interfere greatly with the test. In order to overcome this error, various methods have been employed. It was proposed to extract the natural antisheep amboceptor by placing the serum in contact with sheep's cells and letting it stand in the ice box. This, however, is a laborious process and sometimes partial hemolysis takes place, which interferes more or less with the results. Barium sulphate has been used to absorb the natural antisheep amboceptor and, while this is accomplished, Noguchi and Bronfenbrenner<sup>16</sup> have shown that the process also removes some of the syphilitic complement binding substance and is, therefore, undesirable.

Certain workers have titrated the serum to determine the exact amount of natural antisheep amboceptor present, and have added artificial amboceptor to make up the deficiency. This procedure is satisfactory when the amount of natural antisheep amboceptor is not in excess of the required amount. Other investigators have attempted to overcome the error of natural antisheep amboceptor by utilizing the cells of other animals than the sheep, for which human sera contain less natural hemolytic amboceptor.

Thus, Detre and Brezovsky<sup>17</sup> used a hemolytic system of horse cells and horse hemolytic amboceptor; Tschernogubow<sup>18</sup> used guinea pig cells; Browning and McKenzie,<sup>19</sup> ox cells; Foix,<sup>20</sup> rabbit cells; Boas,<sup>21</sup> goat cells; and Jobling,<sup>22</sup> hen cells.

However, the most rational method of overcoming the error of natural antisheep amboceptor is the use of human cells as proposed by Noguchi,<sup>23</sup> as there is no natural antihuman hemolytic amboceptor in human serum.

#### MODIFICATIONS OF TECHNIC

While all of the modifications of the Wassermann test depend upon the principle of complement fixation, the methods of applying the principle vary greatly.

*Modification of Bauer.*<sup>24</sup>—In his modification of the complement fixation test for syphilis, Bauer uses all of the factors from the same source as Wassermann, with the exception of the amboceptor. That is, the complement is fresh guinea pig serum; the corpuscles are washed sheep cells; the antigen is aqueous extract of syphilitic fetal liver, and the patient's serum is inactivated to destroy the native

complement before using. For amboceptor Bauer relies upon the natural antish sheep amboceptor present in most human sera.

*Modification of Hecht-Weinberg.*<sup>25</sup>—In this test, not only is the natural antish sheep amboceptor made use of, but the native complement is made to suffice. Washed sheep cells are employed, the antigen is an alcoholic extract of human heart, while the patient's serum is employed in the fresh state. Four small tubes are used for each test and are set up as follows: Tube 1.—0.02 c.c. serum (1 drop) and 0.08 c.c. (4 drops) of 1:50 dilution of antigen. Tube 2.—0.02 c.c. serum and 0.08 c.c. of 1:100 dilution of antigen. Tube 3.—0.02 c.c. serum and 0.08 c.c. of 1:200 dilution of antigen. Tube 4.—0.02 c.c. serum and 0.08 c.c. normal salt solution.

The tubes are first placed in an incubator for one-half hour, or in the water bath at 37° C. for ten minutes. Following this, 1 c.c. of 1 per cent dilution of washed sheep's cells is added to each tube, shaken and replaced, either in the incubator for one-half hour, or in the water bath for ten minutes.

Tube 4, which contains no antigen, must show complete hemolysis or the test is worthless. If it does not show complete hemolysis, it is an indication that the patient's serum does not contain a sufficient quantity of the complement-amboceptor combination. A strongly positive test is indicated by complete inhibition of hemolysis of all other tubes, while the varying degrees of positive tests are indicated by varying amounts of hemolysis in the first three tubes.

*Modification of Hecht-Gradwohl.*<sup>26</sup>—In 1914 Gradwohl proposed a modification of the Hecht-Weinberg test which he describes as follows:

“Place in a rack fourteen small test tubes. The first ten of these tubes are used to determine the hemolytic index of the suspected blood. By this we mean the exact amount of hemolytic amboceptor present in the given blood-serum. The last four tubes are used in the actual test. Add 0.1 c.c. of fresh unheated patient's blood serum to each of the first ten tubes. Then add decreasing amounts of normal salt solution to these tubes, beginning with 1 c.c., then 0.9, 0.8, 0.7, 0.6, 0.5, 0.3, 0.2, 0.1 c.c. to the succeeding nine tubes. Next add increasing amounts of fresh 5 per cent suspension of sheep's blood, starting with 0.1 c.c. and ending with 1 c.c. Place the rack in the water bath for one-half hour. The tube which last shows complete hemolysis constitutes our ‘hemolytic index’; if it is Tube 4,

our index is 4 because this tube has received 0.4 c.c. of sheep's corpuscles. The index determines the amount of sheep's corpuscles to be added to the last four tubes. The first three tubes (11, 12 and 13) constitute the tubes for the actual test, while the last tube in the rack (Tube 14) serves as our serum control tube. Tubes 11, 12 and 13 receive, therefore, the patient's serum, the proper amount of sheep's corpuscles (dependent on the hemolytic index) rising strength of antigen, but no complement and amboceptor. Tube 14 receives only sheep's corpuscles but no antigen. In our technic we use 0.1 c.c. of a diluted antigen determined by titration in Tube 11, 0.15 c.c. antigen in Tube 12, and 0.2 c.c. in Tube 13. In order to equalize the volume of fluid in all these tubes, we add 0.2 c.c. normal saline to Tube 11, 0.15 c.c. to Tube 12, and 0.1 c.c. to Tube 13, and 0.3 c.c. to Tube 14. The tubes are then agitated and placed in the water bath for half an hour. These last four tubes are filled at the time we make the addition to the first ten and are left with them in the water bath for one-half hour and for fixation of complement, the rack is then taken out and the hemolytic index computed. If the index is low, say from 1 to 4, we add 0.1 c.c. of sheep's blood to the last four tubes. If the index is between 5 and 7, we use 0.15 c.c. sheep's blood and if it is between 7 and 10 we use 0.2 c.c. In our experience in this country we have never found an index above 10, although in France it is not uncommon to obtain an index of 15 or 17.

"If the patient's serum has an index below 3, we regard the reaction as of doubtful value. If it is above 3, we regard it as absolute. The reaction is read off exactly as in the Wassermann; that is, inhibition or noninhibition of hemolysis."

*Modification of Stern.*<sup>27</sup>—Margaretta Stern proposed a method of complement fixation in testing for syphilis which utilizes the native complement present in the serum to be tested, which is, of course, used in the fresh, noninactivated state. As antigen, alcoholic extract of liver or heart is employed, but the quantity is used in  $\frac{2}{5}$  to  $\frac{1}{5}$  of the usual amount to avoid false positive reactions. Sheep's cells are employed and immune rabbit-sheep amboceptor, which is used in three or four times the amboceptor unit.

*Modification of Tschernogubow.*—Tschernogubow<sup>28</sup> in 1909 proposed a modification of the Wassermann test in which he advocated the use of human corpuscles obtained from the patient's blood. The

complement is the native complement of the patient's blood (not serum). The antigen is dried, syphilitic liver, extracted before use and the amboceptor is antihuman hemolytic amboceptor, the source of which is not stated.

In performing the test, the patient's blood is collected in sodium citrate solution to prevent clotting, and the antigen is added. It will be seen that the mixture contains complement, erythrocytes (unwashed), antigen and "syphilitic antibody," if present. After a suitable incubation period, the antihuman amboceptor is added, incubation is continued and the test is positive or negative, depending upon whether or not hemolysis has taken place.

Later, Tschernogubow<sup>18</sup> abandoned this test for a technic which is radically different. In this later modification, the corpuscles are those of the guinea pig, thoroughly washed; the antigen is the alcoholic extract of normal liver, while both the complement and amboceptor are derived from the patient's serum, which, of course, must be tested in the fresh state. Tschernogubow recommends collecting the blood from the finger and placing 0.1 c.c. in a test tube with 0.9 c.c. salt solution and 0.1 c.c. in 0.9 c.c. of a 0.5 per cent extract of normal liver. These tubes are now centrifugalized and the clear fluid pipetted off and placed in other tubes. These are then placed in the thermostat at 38° C. for one-half hour after which 0.25 of a 5 per cent dilution of washed guinea pig corpuscles are added to each tube and the incubation continued for one hour.

*Modification of Brezovsky.*<sup>17</sup>—Detre and Brezovsky proposed a modification of the Wassermann test in which thoroughly washed horse erythrocytes are used. The amboceptor is immune horse-rabbit serum; the complement is obtained from fresh rabbit serum and the patient's serum is added in definite quantity, inactivated before use. The technic of performing the test is similar to that of the original Wassermann.

*Modification of Browning and McKenzie.*<sup>19</sup>—Browning and McKenzie introduced a method of complement fixation for testing for syphilis differing from the original Wassermann but little except that the ox-rabbit hemolytic system is employed instead of the sheep-rabbit system. Alcoholic extract of human heart is used as antigen instead of aqueous extract of syphilitic fetal liver.

*Modification of Boas.*<sup>21</sup>—Boas also proposed a method which differs from the original Wassermann only in the hemolytic system and the

antigen used. This worker employed the goat-rabbit hemolytic system and the alcoholic extract of human heart as antigen.

*Modification of Foix.*<sup>20</sup>—This investigator proposed a system similar to Tschernogubow's later system, using washed rabbit corpuscles, and utilizing the native complement and amboceptor in the patient's serum which is used in the fresh state. The antigen is alcoholic extract of various organs.

*Modification of Noguchi*<sup>23</sup>—Probably no other investigator has done more to popularize and place on a firm basis the complement fixation test for syphilis, than Noguchi. His method of procedure, with at most slight modification, has been used more extensively, especially in this country, than any other method.

Aseptic technic is not necessary, although thorough chemical cleanliness is prescribed. Noguchi's conception was to so modify the Wassermann reaction as to place it within the hands of the practicing physician. He, therefore, prescribed the preservation of antigen, amboceptor and the complement by drying on filter paper. This, however, except for amboceptor, was soon found to be unsatisfactory and was abandoned.

As stated above, this investigator uses the antihuman hemolytic amboceptor, the acetone insoluble liquids as antigen, and the patient's serum in noninactivated state. For complement, he uses a 40 per cent solution of fresh guinea pig serum in normal saline and his corpuscle suspension consists of a 1 per cent solution of washed human corpuscles in normal saline.

The antigen and amboceptor (either a liquid or dried on filter paper) should be titrated before use. The alcohol stock solution of antigen is made into an emulsion by diluting 1 to 10 with normal salt solution. According to Noguchi, an antigen is suitable for use if 0.4 c.c. of this emulsion will not produce hemolysis when added to the dose of corpuscle suspension or interfere with hemolysis when added to the complete hemolytic system, and will bind complement with a known luetic serum in a dose of 0.2 c.c.

The method of titrating amboceptor is similar to that described under the Wassermann technic, except that the amboceptor is dried on filter paper and increasing numbers of small regular squares of this are added to the tubes.

A test tube rack having two parallel rows of holes is secured. Two tubes, one in the front row and one in the rear row of holes, are used

for each serum to be tested and two each for positive and negative controls. Tubes 10 mm. by 10 cm. are recommended.

One drop from a capillary pipette of noninactivated serum is placed in each of the two tubes of the test. (Four drops of inactivated serum should be used.) The positive and negative sera are used in like amounts or the negative control tubes need contain no serum. To each tube is added 0.1 c.c. of complement (40 per cent guinea pig serum), and to the front tube 0.1 c.c. of the antigen emulsion. (If the antigen is up to Noguchi's standard, it will be seen that at least 5 antigenic units are used.) Finally, to each tube is added 1 c.c. of the corpuscle suspension. Incubation is carried out for one hour at 37° C. or for thirty minutes in a water bath at a like temperature.

Following this a slip of amboceptor paper containing 2 units is added to each tube and incubation continued for two hours, or one hour if the water bath is used. The tubes are now removed and kept for two hours at room temperature, when the results are recorded.

All of the tubes in the rear row should complete hemolysis as well as the front tube of the negative control. The front tube of the positive control should show complete inhibition of hemolysis and the front tubes of the sera being tested will indicate positive or negative, depending upon whether there is hemolysis or inhibition.

Should any of the rear tubes show partial or complete inhibition of hemolysis it is an indication that anticomplementary substances are present in the serum. These substances usually are thermolabile and may be destroyed by inactivation at 55° C. for thirty minutes when the serum may again be tested or a fresh specimen secured.

*Modification of Thompson.*<sup>29</sup>—In 1913 I proposed a modification of the syphilis test which partakes somewhat of the original Wassermann and somewhat of the Noguchi technic. The human-rabbit hemolytic system is used; the complement is fresh guinea pig serum; the antigen is alcoholic extract of syphilitic fetal liver, and the patient's serum is used inactivated in 0.1 c.c. amounts, while the total volume in the tube is made up to 2.5 c.c. The amboceptor is used in the liquid form, titrated before each test and used in doses of two units.

As already noted, Wassermann and Noguchi and others, also employ amboceptor in two unit doses. This is for the purpose of overcoming the anticomplementary substances present to a greater or lesser extent in all sera and antigen. This procedure seemed inae-

curate in that the worker does not *know* that twice the amount of the amboceptor unit will just produce hemolysis in the presence of a negative serum and antigen. He also does not know but that when a small amount of complement is bound by a slightly positive serum enough complement may be left to produce complete hemolysis and a weakly positive test be changed to a negative.

In order to overcome these objections, I adopted the following method of titrating amboceptor<sup>30</sup>: Actual test conditions are imposed throughout.

Fifteen tubes are required for the actual titration, and eight tubes for controls. These should be chemically clean, but not necessarily sterile. Into each of the fifteen tubes is placed 0.1 c.c. of known negative serum, or better still, a like amount of the pooled sera of several known nonluetic individuals, 0.1 c.c. of complement, 1 unit of previously titrated antigen (diluted so that 1 unit equals 0.1 c.c.) and the amount of normal salt solution required to bring the total volume up to 2.5 c.c. after the addition of the amboceptor and corpuscles. The tubes are now incubated for one-half hour in the water bath at 37° C., after which the amboceptor and corpuscles are added.

Tube 1 receives 0.5 c.c. of a 1 to 10,000 dilution of amboceptor serum in salt solution and the mount is increased in each tube until tube 15 contains 1 c.c. of a 1 to 1000 dilution or 0.01 c.c. of pure serum. The eight control tubes receive the various reagents as indicated in Table I, and if all reagents are working properly the results will be as indicated.

Table I also indicates the results of the titration of a good amboceptor. It will be seen that Tubes 1 and 2 show no hemolysis. Tubes 3, 4, 5, 6 and 7 show partial hemolysis, which varies from slight to almost complete, and that the remainder of the tubes of the titration test show complete hemolysis. Tube 8 containing 0.3 c.c. of a 1 to 1000 dilution, is the tube which contains the least amount of amboceptor which shows complete hemolysis, and therefore 0.003 c.c. is the unit.

*In the actual performance of the test 1 unit and only 1 unit is employed.*

It has been objected that sera vary in their anticomplementary effect, and that a false positive may result from using an amount of amboceptor, which, while it will completely hemolyze the corpuscles when used with the titration serum, will not do so with all the negative

TABLE I  
TITRATION OF AMBOCEPTOR

TUBE	SER.	COMP.	AMT.	NACL.	AMBOCEPTOR	CORP.	TOTAL	RESULT
1	0.1	0.1	0.1	1.2	0.5 of 1 to 10,000	0.5	2.5	NH
2	0.1	0.1	0.1	1.1	0.6 " 1 " 10,000	0.5	2.5	NH
3	0.1	0.1	1.0	1.0	0.7 " 1 " 10,000	0.5	2.5	PH
4	0.1	0.1	0.1	0.9	0.8 " 1 " 10,000	0.5	2.5	PH
5	0.1	0.1	0.1	0.8	0.9 " 1 " 10,000	0.5	2.5	PH
6	0.1	0.1	0.1	1.6	0.1 " 1 " 1,000	0.5	2.5	PH
7	0.1	0.1	0.1	1.5	0.2 " 1 " 1,000	0.5	2.5	PH
8	0.1	0.1	0.1	1.4	0.3 " 1 " 1,000	0.5	2.5	H
9	0.1	0.1	0.1	1.3	0.4 " 1 " 1,000	0.5	2.5	H
10	0.1	0.1	0.1	1.2	0.5 " 1 " 1,000	0.5	2.5	H
11	0.1	0.1	0.1	1.1	0.6 " 1 " 1,000	0.5	2.5	H
12	0.1	0.1	0.1	1.0	0.7 " 1 " 1,000	0.5	2.5	H
13	0.1	0.1	0.1	0.9	0.8 " 1 " 1,000	0.5	2.5	H
14	0.1	0.1	0.1	0.8	0.9 " 1 " 1,000	0.5	2.5	H
15	0.1	0.1	0.1	0.7	1.0 " 1 " 1,000	0.5	2.5	H
16	0.0	0.1	0.1	0.9	1.0 " 1 " 1,000	0.5	2.5	H
17	0.0	0.1	0.1	0.8	1.0 " 1 " 1,000	0.5	2.5	H
18	0.0	0.1	0.1	1.8	.....	0.5	2.5	NH
19	0.0	0.1	0.0	1.9	.....	0.5	2.5	NH
20	0.0	0.0	0.1	0.9	1.0 " 1 " 1,000	0.5	2.5	NH
21	0.0	0.0	0.1	1.9	.....	0.5	2.5	NH
22	0.0	0.0	0.0	1.0	1.0 " 1 " 1,000	0.5	2.5	NH
23	0.0	0.0	0.0	2.0	.....	0.5	2.5	NH

sera tested, owing to a greater amount of anticomplementary substance in the latter. That sera do vary in their anticomplementary effect is undoubtedly true, but it is hard to believe that any serum to be tested will contain more anticomplementary substances than the pooled sera of several known nonluetie individuals. In fact, this has been found to be true in practice, especially when the pooled sera are obtained as in my laboratory. Here the practice has been to preserve all negative sera and just before titrating to pool a sufficient quantity of those sera remaining uncontaminated and inactivate. This inactivation destroys to a large extent the anticomplementary substances. If there is any discrepancy between the anticomplementary substances contained in the titrating sera and the sera to be tested, there certainly would be more of such substances in the titrating sera, as the sera to be tested are usually fresh.

One of the early objections to the Wassermann test was the fact that fresh guinea pig serum was essential, which in the case of small laboratories was sometimes hard to obtain. Noguchi attempted to overcome this objection by preserving complement dried on filter paper but this soon proved unsatisfactory. Complement may be



frozen and preserved at a low temperature ( $-15^{\circ}$  C.) for several months. H. L. McNeil<sup>31</sup> suggests placing the complement in a tightly stopped test tube in a thermos bottle filled with salt and ice. Austin<sup>32</sup> advocates making a 40 per cent dilution of the guinea pig serum with 25 per cent sodium chloride solution. Then in his tests he uses 0.6 per cent sodium chloride or 0.081 gram. The entire sodium chloride that by so doing he gets approximately 0.9 per cent in his tubes.

In order to secure accuracy of dilution, as well as to secure a suitable dilution for titration, I have devised the following technic for preserving complement:<sup>33</sup>

An 8.1 per cent sodium chloride solution is prepared and autoclaved. Fresh guinea pig serum is diluted with this solution 1 to 1, and sealed in small tubes, 2 c.e. to the tube. It will be seen that each tube contains 1 c.e. of pure guinea pig serum containing (supposedly) 0.9 per cent of sodium chloride or 0.009 gram, and 1 c.e. of an 8.1 per cent sodium chloride or 0.081 gram. The entire sodium chloride content of each tube is 0.09 gram, corresponding to the quantity each 10 c.e. of normal salt solution should contain. Therefore, in order to make a solution containing 0.9 per cent sodium chloride, it is only necessary to add 8 c.e. of distilled water to the contents of each tube and a 1 to 10 dilution of guinea pig serum is produced.

It has been the custom in my laboratory to bleed from the heart three to five good sized guinea pigs at one time, securing 20 to 50 c.e. of blood, which lasts from ten days to two weeks, depending upon the number of tests being made. While the complement usually is not kept longer than two weeks, some six weeks old has been used and was apparently as active as ever.

*Modification of Bronfenbrenner and Schlesinger.*<sup>34</sup>—Quite recently these investigators have proposed a modification of the Wassermann which they especially recommend for hospital routine. The human-rabbit hemolytic system is employed; the complement is that naturally present in the patient's serum, plus guinea pigs serum when necessary; and the antigen is the acetone insoluble lipoids of Noguchi and Bronfenbrenner.

Several features of this test are unique and deserve special mention. The corpuscle suspension is prepared by shaking the clot of freshly collected human blood with physiological salt solution in a test tube, following which the liberated cells are filtered through filter paper. The cells are then washed free from serum in the usual manner and

the density of the suspension determined by means of a Sahli hemoglobinometer. The corpuscle suspension is tested the same as whole blood, the average reading for the latter being considered 75. The following example is given:

"The reading with the unknown suspension may be 50. This means that the suspension is 50/70 or 66.6 per cent of the whole blood. To make a 10 per cent suspension, dilute 1.0 c.c. of the stock up to 6.66 c.c. with physiological salt solution. To make a 50 per cent suspension dilute 5 c.c. to 6.66 c.c. and so on."

The amboceptor, which as stated above is the human-rabbit immune serum, is dried on paper and is titrated against fresh human serum, using 0.025 c.c. of serum as one unit. In the tests when a sufficient quantity of complement is not contained in this amount of serum, the deficiency is made up by adding guinea pig serum. The guinea pig serum is titrated against the unit of amboceptor and the resulting unit is termed human equivalent unit (HEU) as it is equivalent to the amount of complement found in 0.025 c.c. of average fresh human serum.

The test itself is performed in two stages, viz., a presumptive test and a test proper. The presumptive test is made by placing 0.05 c.c. of each serum to be tested in a tube and the total volume brought up to 0.9 c.c. with salt solution. The tubes are now placed in their ice box overnight, (18 hours) and are then placed in the water bath for one-half hour. During this process the cells are sensitized by adding amboceptor diluted so that 10 hemolytic units represented by 0.8 c.c. to the cells in the proportion of 0.8 c.c. amboceptor solution to 0.2 c.c. of 50 per cent red blood cells and incubating one-half hour in the water bath. At the end of the half hour 0.1 c.c. of this suspension of sensitized cells is added to each of the tubes containing the sera to be tested and incubation continued for another half hour. Complete hemolysis in a tube is an indication that the test is negative. Inhibition or partial hemolysis is an indication either that there is insufficient complement in the serum used (0.05 c.c.) to cause hemolysis or that although there might have been sufficient complement present, the serum also contains specific antibodies which binds the complement.

The next procedure is the determining which of the two latter possibilities are operating. This is done by titrating the complement content of the human serum by placing 0.025 c.c. and 0.05 c.c. in two

tubes respectively, adding 0.1 c.c. of sensitized cells and bringing the total volume up to 1 c.c. with salt solution. The following table indicates the possibilities of the titration.

TABLE II

VARIOUS POSSIBILITIES IN THE DEGREE OF HEMOLYSIS OBTAINED IN COMPLEMENT TITRATION EXPERIMENT. (DETERMINED BY MADSEN SCALE.)		NUMBER OF UNITS OF COM- PLEMENT PRESENT IN 0.05 C.C. OF SERUM AS DETER- MINED BY TITRATION
0.02 c.c. Serum	0.05 c.c. Serum	
0% hemolysis	0% hemolysis	0.0
0% "	50-70% "	0.5
0-50% "	70-100% "	1.0
50-70% "	100% "	1.5
75-100% "	100% "	2.0

*Test Proper.*—Into each of two tubes 0.05 c.c. of the serum to be tested is placed, a sufficient quantity of the guinea pig serum (the amount having been determined by previous titration) to bring the total quantity of complement up to two units and one unit of antigen into one of the tubes. The total volume in each tube is next brought up to 0.9 c.c. with salt solution and the tubes incubated in the water bath at 37° C. for one-half hour. At the end of this time each tube receives 0.1 c.c. of sensitized cells and the incubation is continued one-half hour, when the results are read.

#### OBJECTIONS TO THE VARIOUS METHODS OF PERFORMING THE COMPLEMENT FIXATION TEST FOR SYPHILIS

*Wassermann's Original.*—Several serious objections present themselves when considering the original Wassermann test. The most glaring is the use of the sheep hemolytic system, which, as pointed out above, interferes with the test on account of natural antisheep amboceptor in nearly all human sera.

The second objection is the use of the aqueous extract of fetal syphilitic liver, which is not stable and is difficult to obtain. It is understood, of course, that many workers employ the original Wassermann technic with the exception of the antigen, using other antigens, when naturally the objections just mentioned are not valid.

A third objection to the original Wassermann tests is the employment of inactivated serum, for, as has been pointed out by Noguchi,<sup>23</sup> not only is the native complement of a serum destroyed by the process

of inactivation, but the specific antibody is also reduced to one-fourth or one-fifth of the original, rendering the test less delicate.

A fourth objection to the use of the original Wassermann is the necessity of keeping guinea pigs so that the serum may be fresh for the complement. As stated above, this objection has been partially overcome by the methods outlined for preserving the complement.

A final objection to the original Wassermann technic is the large quantities of reagents employed. This has been overcome, however, by some workers by using fractions of the doses of each of the reagents.

*Modification of Bauer.*—This modification is open to most of the objections enumerated for the original Wassermann, as well as to the much more serious objection that the natural antishoop amboceptor present in nearly all human sera is such a variable quantity that to rely upon it in the manner proposed makes the test most inaccurate. Furthermore, Noguchi<sup>23</sup> has shown that the use of alcoholic extracts with noninactivated sera may lead to false positives.

*Modification of Hecht-Weinberg.*—This test, as stated above, uses both the natural antishoop amboceptor and the natural complement of the serum to be tested. No attempt is made to titrate either of these factors, and if, as sometimes occurs, no natural antishoop amboceptor is present, or the complement-amboceptor combination is insufficient to cause complete hemolysis, the test is worthless.

*Modification of Hecht-Gradwohl.*—One objection to this modification is the large number of tubes needed for each test, and consequently, the greater amount of labor entailed. Another objection is that although the complement-amboceptor combination is titrated, or, as Gradwohl terms it, the "hemolytic index" is determined, the strength of these two factors is not determined separately, and in the performance of the test there is danger of error.

Finally, as Gradwohl himself points out, if the "hemolytic index" is below 3, the test is of doubtful value.

*Modification of Stern.*—In Stern's modification, no attempt is made to titrate the native complement, but the antigen is used in 2/5 to 1/5 of the usual amounts to avoid false positives, and as a further precaution, the amboceptor is employed in three or four times the amboceptor unit. This is obviously very inaccurate and unscientific.

*Modification of Tschernogubow.*—In his first modification, this worker made no attempt to titrate his reagents, and for this reason

it is very unreliable. The danger of false positives, is somewhat overcome by using very large quantities of amboceptor, but the danger of false negatives is made greater. Tschernogubow apparently realizes the inherent defects in this system, as he soon abandoned it.

His second modification, however, is not much of an improvement over the first one, as he does not titrate his reagents in this test either. Both tests are liable to give false positives on account of the use of alcoholic extract with noninactivated serum.

*Modification of Detre and Brezovsky.*—This modification is open to the same objections, although perhaps the natural antihorse amboceptor in the average human serum is not as great as the natural antisheep amboceptor. This, however, is more than overcome by the greater difficulty of securing horse corpuscles.

A further objection is the fact that the complement of rabbit serum is much more variable than that of guinea pig serum.

*Modification of Browning and McKenzie.*—The same remarks apply to this modification as to that of Detre and Brezovsky, except that guinea pig serum is used as complement instead of rabbit serum and is, therefore, more reliable.

*Modification of Boas.*—Obviously there is no advantage in using the antigoat hemolytic system instead of the antisheep system, and this test is therefore open to all of the objections of the original Wassermann.

*Modification of Foix.*—As this test is similar to Tschernogubow's later system, it is open to practically the same objections.

*Modification of Noguchi.*—The main objections to this modification are the small quantity of patient's serum employed which in weakly positive cases may not contain a sufficient amount of syphilitic antibodies to cause binding of complement, and that guinea pig serum is necessary.

*Modification of Thompson.*—The objections which I now find in the modification I proposed in 1913, are that the serum used is inactivated, which process, as pointed out above, destroys some of the syphilitic antibodies, and that guinea pig serum is necessary.

*Modification of Bronfenbrenner and Schlesinger.*—In this test, while the authors rely, in a majority of cases, on the native complement present in the patient's serum, and thus do away with the destruction of a part of the syphilitic antibodies, in some instances they must use guinea pig serum. A further objection is that such a

small quantity of patient's serum is employed that in weakly positive tests there may not be sufficient antibodies present to bind complement.

#### A NEW MODIFICATION

After seven year's experience with the various modifications of the complement fixation test for syphilis, I have devised a method which is simple, reliable, and open to none of the objections of the methods already proposed. The patient's serum is used in the fresh, noninactivated state in quantities sufficient to insure the presence of sufficient syphilitic antibodies to bind complement when such antibodies are present at all; the complement is derived from the patient's serum and is accurately titrated; the amboceptor is the serum of rabbits immunized against human red blood cells; the antigen is the acetone insoluble lipoids of Noguchi and Bronfenbrenner, while the corpuscles are thoroughly washed human erythrocytes from any convenient source, usually from one of the patients whose serum is being tested.

*Patient's Serum.*—As stated above the patient's serum is used in comparatively large quantities. This makes it desirable to collect from 10 to 15 c.c. of blood. It may be argued that this is an objection, but as the best method of collecting blood, when more than a few drops is desired is by venipuncture, and as it is as easy to collect 10 to 15 c.c. as 5 c.c., this objection is not valid. The most satisfactory method of collecting blood by venipuncture which I have ever seen, is by the use of a special platinum needle which has a square "collar" attached to it, as shown in Fig. 1. A platinum needle is used because it may be quickly and absolutely sterilized, by placing in a Bunsen flame for a few seconds. Further, the blood will not clot as rapidly in such a needle as in a steel one. The needle is caught at the collar with a pair of artery forceps which have had their tips bent at right angles, the collar preventing the needle from being dented. A test tube of convenient size, or a centrifuge tube, which has been sterilized by boiling in salt solution, or has been rinsed with sterile salt solution after other sterilization, is placed in the right angle of the forceps so that the proximal end of the needle projects into the mouth of the tube which is held against the forceps either by a rubber band or by the right hand of the operator (Fig. 2).

The reason for using salt solution in the tube is that the serum separates more quickly, in greater quantity, and without hemolysis



Fig. 1.

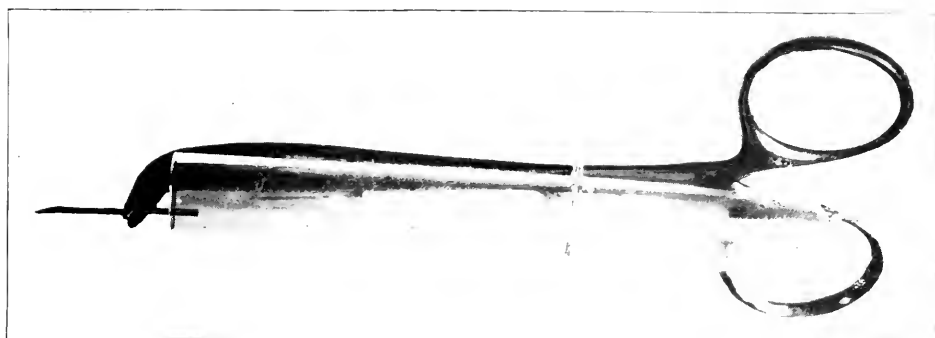


Fig. 2.



Fig. 3.





in a tube so prepared than in one not so prepared. A tourniquet is placed around the arm of the patient in the usual way, and after sterilizing the area, the needle is thrust into one of the veins of the elbow, the forceps holding it steady and furnishing a convenient handle (Fig. 3). The blood usually will flow in a stream, and 10 to 15 c.c. may be collected in a very few seconds. By holding the needle under running water the blood will be washed out and it may be resterilized. A 19 guage needle is best for ordinary purposes, but different sizes may be used as occasion demands.

After collection, the blood may be placed in the ice box for an hour or two after which rapid centrifugalization will separate the clot, and the clear serum may be poured off. This should be placed in the ice box until used, which should be within 24 hours.

If it is desirable to keep a serum longer it may be placed in a tube in a thermos bottle filled with salt and ice. If this is changed daily the serum will keep its complement qualities a week or ten days.

*Amboceptor.*—One of the main objections to the use of the human hemolytic system in the complement fixation test for syphilis, is the claim of many workers that a good antihuman amboceptor is difficult to produce. The method of producing antihuman amboceptor recommended by Noguchi<sup>23</sup> and employed by the majority of workers, is to inject large, healthy rabbits intravenously with 4 c.c., 3 c.c., 4 c.c., 3 c.c. and 4 c.c. at four or five day intervals and to bleed on the ninth or tenth day following the last injection.

This method of injection is not always productive of a good amboceptor and often leads to the death of the rabbit from anaphylaxis. In order to overcome this latter objection, Bronfenbrenner and Schlesinger<sup>34</sup> suggest preceding each intravenous injection, beginning with the third one, by a desensitizing intraperitoneal injection of the same cells given one-half hour in advance.

In an attempt to overcome the first objection, that is, the difficulty of securing a strong amboceptor, I tried out various other methods which have been suggested by different workers for the production of antishoop amboceptor. The method which proved to give the most powerful antihuman amboceptor is the one which Coca<sup>35</sup> states yields the most powerful antishoop amboceptor. It consists of giving daily intravenous injections of 0.1 c.c. of washed human corpuscles over a period of several weeks, usually three to four. After the rabbits have been injected for three weeks a small quantity of blood is with-

drawn either from the heart or from a marginal ear vein and the hemolytic effect of the serum tested. If it proves of sufficient strength, the rabbit is bled on the third day, about 25 c.c. being withdrawn from the heart, and again on the fourth day, an equal amount being collected. This usually is not fatal to the rabbit, and the amboceptor withdrawn on the fourth day is as strong as that withdrawn on the third day. If the blood serum withdrawn for titration is not of sufficient strength, the injections are resumed and continued until it is of sufficient strength, tests being made at weekly intervals.

The blood is collected in sterile centrifuge tubes which have been rinsed in sterile salt solution and placed in the ice box overnight. The following morning the tubes are centrifugalized and the clear serum is pipetted off and preserved by adding 0.5 per cent phenol.

*Antigen.*—As stated above, the antigen used in this test is the acetone insoluble lipoids of Noguchi and Bronfenbrenner. This antigen is best prepared from fresh beef heart, and is carefully titrated before use.

*Corpuscles.*—The corpuscle suspension is a 2 per cent dilution of thoroughly washed erythrocytes. The most convenient method of preparing this suspension is to add, at the time of collection for the test, 2 c.c. of whole blood from one of the patients, to a centrifuge tube containing a few c.c. of 2 per cent sodium citrate solution in normal salt solution. The tube is then centrifugalized and the clear supernatant fluid pipetted off. The corpuscles are then washed in the usual manner three times and following the last centrifugalization it will be seen that approximately 1 c.c. of corpuscles remains. To these are added 49 c.c. of physiological salt solution, making a 2 per cent dilution. As the number of corpuscles varies but little in different individuals, except in hematogenous diseases, the corpuscle suspension prepared in this manner is sufficiently constant for practical purposes.

#### TITRATION OF REAGENTS

It has been pointed out above that the titration of the reagents in the complement fixation tests for syphilis is of the utmost importance; in fact, without such titration the test becomes worse than useless.

The first titration is that of the amboceptor and the method is as follows:

Into each of 15 small test tubes are placed 0.2 c.c. of fresh human

serum,\* 0.2 c.c. of the corpuscles suspension, increasing amounts of amboceptor and physiological salt solution to bring the total volume up to 1 c.c. as indicated in Table III.

TABLE III  
TITRATION OF AMBOCEPTOR.

TUBE	SERUM	AMBOCEPTOR	CORP.	NACL	TOTAL	RESULT
1	0.2	0.1 of 1 to 1000	0.2	0.5	1.0	NH
2	0.2	0.2 " 1 " 1000	0.2	0.4	1.0	PH
3	0.2	0.3 " 1 " 1000	0.2	0.3	1.0	PH
4	0.2	0.4 " 1 " 1000	0.2	0.2	1.0	PH
5	0.2	0.5 " 1 " 1000	0.2	0.1	1.0	H
6	0.2	0.6 " 1 " 1000	0.2	0.0	1.0	H
7	0.2	0.7 " 1 " 1000	0.2	0.0	1.1	H
8	0.2	0.8 " 1 " 1000	0.2	0.1	1.2	H
9	0.2	0.9 " 1 " 1000	0.2	0.0	1.3	H
10	0.2	0.1 " 1 " 1000	0.2	0.5	1.0	H
11	0.2	0.2 " 1 " 1000	0.2	0.4	1.0	H
12	0.2	0.3 " 1 " 1000	0.2	0.3	1.0	H
13	0.2	0.4 " 1 " 1000	0.2	0.2	1.0	H
14	0.2	0.5 " 1 " 1000	0.2	0.1	1.0	H
15	0.2	0.6 " 1 " 1000	0.2	0.0	1.0	H

This table also indicates the results of the titration of a good amboceptor. As ordinary amboceptor maintains its strength for several months, it is unnecessary to titrate it very frequently. The smallest amount of amboceptor which causes complete hemolysis of the 0.2 c.c. of corpuscles in the presence of 0.2 c.c. of fresh human serum is doubled and the resulting amount used as the unit for the titration of the complement content of the sera to be tested.

*Titration of Complement.*—This titration is made with each serum and is performed as follows: A series of four tubes is set up and into each is placed one unit of amboceptor, increasing amounts of patient's serum diluted 1 to 1 with physiological salt solution, 0.2 c.c. of corpuscle suspension and sufficient salt solution to bring the total volume up to 1 c.c. as indicated in Table IV.

TABLE IV  
TITRATION OF COMPLEMENT

TUBE	SERUM	AMB.	CORP.	NACL	TOTAL	RESULT
1	0.1	0.1	0.2	0.6	1.0	PH
2	0.2	0.1	0.2	0.5	1.0	H
3	0.3	0.1	0.2	0.4	1.0	H
4	0.4	0.1	0.2	0.3	1.0	H

\*The pooled serum of several individuals or a serum which has been titrated against known amboceptor should be used.

This table also indicates the titration of the average human serum, although marked variations are occasionally found which will be discussed later.

*Titration of Antigen.*—The first factor to be considered in the titration of antigen is the hemolytic effect, and no antigen should be used which of itself, in an amount considerably in excess of the antigenic unit, will cause hemolysis. This is determined by adding to the corpuscle suspension increasing amounts of antigen as indicated in Table V, and incubating the tubes for one hour.

TABLE V  
TITRATION OF ANTIGEN (HEMOLYTIC EFFECT)

TUBE	AMT.	CORP.	NACL	TOTAL	RESULT
1	0.1 of 1 to 5	0.2	0.7	1.0	NH
2	0.2 " 1 " 5	0.2	0.6	1.0	NH
3	0.3 " 1 " 5	0.2	0.5	1.0	NH
4	0.4 " 1 " 5	0.2	0.3	1.0	NH
5	0.5 " 1 " 5	0.2	0.2	1.0	NH
6	0.6 " 1 " 5	0.2	0.2	1.0	NH
7	0.7 " 1 " 5	0.2	0.1	1.0	NH
8	0.8 " 1 " 5	0.2	0.0	1.0	NH

A good antigen as indicated by Table V will show no hemolysis in amounts up to 0.8 c.c. of a 1 to 5 dilution.

The second point to be determined is the anticomplementary effect of the antigen; that is, the largest quantity which will not interfere with hemolysis in the presence of a known negative serum. In a good antigen the effect must be evident in an amount considerably in excess of the antigenic unit. A series of six tubes is prepared into each of which is placed 0.2 c.c. of a known negative serum which has been titrated and found to contain one unit of complement to each 0.2 c.c. of a 1 to 1 dilution; therefore the 0.2 c.c. of serum will contain two units of complement. The antigen is added in increasing quantities and physiological salt solution as indicated in Table VI.

TABLE VI  
TITRATION OF ANTIGEN (ANTICOMPLEMENTARY EFFECT)

TUBE	SER.	AMT.	NACL	AMB.	COM.	TOTAL	RESULT
1	0.2	0.2 of 1 to 10	0.3	0.1	0.2	1.0	H
2	0.2	0.4 " 1 " 10	0.1	0.1	0.2	1.0	H
3	0.2	0.6 " 1 " 10	0.0	0.1	0.2	1.1	H
4	0.2	0.8 " 1 " 10	0.0	0.1	0.2	1.3	H
5	0.2	0.6 " 1 " 5	0.0	0.1	0.2	1.0	H
6	0.2	0.8 " 1 " 5	0.0	0.1	0.2	1.3	PH

The tubes are now incubated in the water bath at 37° C. for one-half hour after which 0.1 c.c. of amboceptor, diluted so that 0.1 c.c. contains one unit, and 0.2 c.c. of the corpuscle suspension are added to each tube, and the incubation continued for one hour.

Table VI denotes the results of the titration of a good antigen. It will be noted that hemolysis is not interfered with in quantities up to 0.6 c.c. of a 1 to 5 dilution.

The final step in the titration of antigen is the determination of the antigenic unit; that is, the smallest amount of antigen in the presence of a known positive serum which will completely inhibit hemolysis. The titration of this factor is identical with the titration of the anti-complementary effect with the exception that a known strongly positive serum is used instead of a negative and the antigen is added in different quantities as shown in Table VII.

TABLE VII  
TITRATION OF ANTIGEN (ANTIGENIC UNIT)

TUBE	SER.	AMT.	NACL	AMB.	CORP.	TOTAL	RESULT
1	0.2	0.2 of 1 to 100	0.3	0.1	0.2	1.0	PH
2	0.2	0.4 " 1 " 100	0.1	0.1	0.2	1.0	NH
3	0.2	0.6 " 1 " 100	0.0	0.1	0.2	1.0	NH
4	0.2	0.8 " 1 " 100	0.0	0.1	0.2	1.3	NH
5	0.2	0.1 " 1 " 10	0.4	0.1	0.2	1.0	NH
6	0.2	0.2 " 1 " 10	0.3	0.1	0.2	1.0	NH

This table also indicates the titration of the antigenic unit of a good antigen. It will be noted that there is no hemolysis with quantities as low as 0.4 c.c. of a 1 to 100 dilution of antigen, and as shown in Table VI there is no anticomplementary effect in quantities up to 0.6 c.c. of a 1 to 5 dilution. It is, therefore, perfectly safe to use 0.1 c.c. of a 1 to 10 dilution in the tests. As this antigen is very stable, it is not necessary to titrate it very frequently.

#### PERFORMANCE OF TESTS

The actual performance of the test with this method, after the titrations are complete, is very simple. Two tubes are required for each serum to be tested and they are arranged in a test tube rack in two rows. It will be noted that in the titration of the complement content of the sera to be tested, a dilution of 1 to 1 is employed. In order to overcome the anticomplementary effect of the antigen, the complement is doubled by placing in each of the two tubes an amount of un-

diluted serum equal to the smallest amount of diluted serum which has been found by titration to cause complete hemolysis. One-tenth of a cubic centimeter of a 1 to 10 dilution of antigen is added to the front row of tubes and sufficient quantity of physiological salt solution to bring the total quantity up to 0.7 c.c. The tubes are now thoroughly shaken and placed in the water bath at 37° C. for one-half hour. Following this, 0.1 c.c. of amboceptor (so diluted that 0.1 c.c. contains one unit) and 0.2 c.c. of the corpuscle suspension are added. After thoroughly shaking the tubes they are replaced in the water bath for one hour, when the results are read.

#### DISCUSSION

The objection to my test may be raised that in titrating each serum, more time is consumed than by other methods. This objection is not valid since the time saved in not using guinea pig serum more than compensates for the extra time employed in titrating each serum.

A further objection may be raised that human sera vary greatly in complement content. This statement is true, but it is also a fact that the vast majority of human sera do not vary greatly in this respect. In over 98 per cent of three hundred sera tested by this method, the complement unit was found to be within the amounts from 0.1 to 0.4 c.c. of a 1 to 1 dilution. When a serum is found which does not show sufficient complement in 0.4 c.c. of a 1 to 1 dilution, a second titration, using larger quantities, is necessary. If even then the serum is found to contain very little complement (one serum required 1 c.c. undiluted to cause complete hemolysis with one unit of amboceptor), it is best to use this serum in 0.2 c.c. quantities and to add to the tubes a sufficient quantity of a known negative serum as complement and proceed as otherwise. The small quantity of complement in the serum being tested may be disregarded.

The same procedure may be employed with spinal fluids which contain no complement.

*Advantages.*—The advantages of my test may be summed up as follows:

1. It does away with the errors which may occur, due to natural amboceptor present, when a hemolytic system other than the human is employed.
2. It does away with the necessity of keeping a sheep or other animal as a source of corpuscles.

3. It uses noninactivated sera which retain all of the specific antibodies, some of which are destroyed by the process of inactivation. Therefore, the test is very delicate.

4. It employs the native complement present in nearly all human sera, thus doing away with the necessity of keeping guinea pigs.

5. The complement is carefully titrated, thus assuring accuracy of results.

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## AORTIC ANEURYSMS AND DILATATIONS\*

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THE condition known as aneurysm deserves some comment. It is said that aneurysms may be *true* or that they may be *false* or *spurious*, by which is meant, on the one hand, that the wall of the sac is composed of all the usual layers of the vessel from which the aneurysm springs,—in other words, that the structure of the sac indicates mere bulging of the vessel wall, that, in fact, a true aneurysm is a dilated portion of the vessel; or, on the other hand, that the wall of the sac is not composed of the usual layers of the vessel from which it springs,—in other words, that the structure of the sac indicates that the bulging is due to some lesion of the vessel wall which permits the blood to collect outside the vessel in a cavity whose lumen is continuous with that of the vessel but whose walls are not those of the vessel. But, as MacCallum says,<sup>1</sup> since we know that in all cases the sac of an aneurysm is formed of a tissue very different from that of the normal arterial wall the distinction is no longer so valid, although the conditions accountable for the two types are not the same. He therefore follows Benda who considers an aneurysm any pathological widening of the arterial lumen caused by a change in its walls, which for a time at least, stands in open communication with its blood stream. For the same reasons I follow Benda.

Aortic aneurysm is accepted by many physicians as an almost certain evidence of syphilitic infection. Occasionally—and only very occasionally, comparatively—dilatation of the aorta comes from other infections, and in still fewer cases they are traumatic. Nevertheless, even in the ancient days of medicine, Lancisi associated this lesion with *morbus gallicus*, and called it *aneurysma gallicus*. Since those times various writers have endeavored to estimate the incidence of lues in relation to aneurysm with the most divergent results, as the following statistical series set forth.<sup>2</sup>

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Klemperer,	Lues responsible in	25	% of the cases.
Fraenkel.	" "	36	% " " "
Puppe,	" "	40.5	% " " "
Heiberg,	" "	41.8	% " " "
Bramwell, Thieberg,	" "	50	% " " "
von Noorden,	" "	54	% " " "
Gerhardt,	" "	56	% " " "
Schutz,	" "	64	% " " "
Welch,	" "	66	% " " "
Étienne,	" "	69	% " " "
Malonsen,	" "	80	% " " "
Haupeln,	" "	82	% " " "
Backhaus, Hiller	" "	85	% " " "
Rasch,	" "	92	% " " "

Osler believes that aneurysm in a man or woman under 30 years of age is almost to be regarded as presumptive evidence of syphilis. My own experience leads me to believe that the higher percentages are more nearly true than the lower ones, and that this is especially true in cases below the age of fifty. It is realized that the diffuse atherosclerosis which is seen so frequently after the age of fifty sometimes leads to aortic dilatation of a rather diffuse type, and that it may be the starting point of focal dilatations, but the whole anatomic picture in such cases is quite essentially different from that in the specific cases and the instances are comparatively few. Lues, to my mind, is the most frequent cause of damage to the vascular walls that results in aneurysm.

The luetic virus, however, does not always result, in the aorta, in the appearance of a typical aneurysm. Sometimes its effect is a diffuse dilatation of the vessel, sometimes it is an irregular dilatation giving the impression of two or more fusiform aneurysms. Sometimes it results in a typical fusiform aneurysm, while in still other instances sharply focal lesions lead to the formation of one or more saccular aneurysms. The form the dilatation takes seems to depend upon the extent of the syphilitic inflammatory process. When infection is focalized in the aorta a focal bulging tends to be produced by heightened blood pressure. When the infection of the aortic wall is diffuse, a "dilated aorta" follows. The following cases form a series in which the various aortic dilatation effects of syphilis are illustrated.

#### CASE I

This case illustrates the type of diffuse aortic infection in which the vessel is dilated.

E.D., Hospital No. A-7898, a white male, married, aged 46, a bartender,

was admitted to the Cincinnati General Hospital, November 28, 1916, in a delirious condition.

*Family History.*—The family history is unimportant.

*Past History.*—The patient had mumps at the age of 1½ years and again at 6 years of age. He had whooping cough at 5, diphtheria at 15, measles at 28. At 9, he had typhoid fever. He had pleurisy at the age of 23. In childhood he had sore throat every winter. Five years ago he had acute arthritis in the left foot and hip and was confined to the house 27 days. He has been subject to occasional dizzy spells all his life. During his adult life he has had tonsillitis nearly every winter. The patient says he has had shortness of breath on exertion for 20 years. Last August for a period of about 2 weeks he had night sweats. The gastro-intestinal tract has always been negative in regard to symptoms, but about a month ago he began to have a dull ache in the epigastric region with an occasional sharp shooting pain running down the left thigh and leg. This pain bore no relation to meals. The patient had gonorrhea at the age of 17. He has smoked and chewed all of his life. He chews three packages of scrap tobacco in 2 days. He has been a regular drinker since he was 16 years of age and has kept bar for 8 years. During this time he has taken from 10 to 20 whiskeys a day. Two and one-half years ago he had delirium tremens.

*Present Illness.*—On November 26th, at 7 p. m. the patient began vomiting a sour, whitish, slimy material. About an hour later he vomited a second time and had a slight headache. The patient says the vomitus has been black and red at times. Previously the patient stated that he vomited about a pint of blood four days ago and in all vomited about ten times that day. He took a cathartic and had frequent stools which he noticed were black. The vomiting has been growing less in the last few days.

*Physical Examination.*—The patient is a fair sized man. His face is flushed. There is a coarse tremor of the hands. He is making motions with his hands as if pushing and says that he is pushing rats away. He also remarked that he was catching roaches and crabs on the bed. The tongue is clean. There is pyorrhea alveolaris. The teeth are carious. The lungs are hyperresonant throughout. The anteroposterior diameter of the chest is increased. The ribs are flaring. The breath sounds are diminished.

Heart: Relative dullness extends 2.4 cm. to the right in the 4th, 8.5 cm. to the left in the 5th. The sounds are regular, of fair quality. There are no murmurs. The aortic second sound is accentuated. The pulse is regular in force and rhythm. Tension is increased. The vessels are thickened and moderately tortuous.

The abdomen is on the level with the ribs. Respiratory movements are free. The liver is felt three fingerbreadths below the costal margin, in the anterior axillary line. The spleen is not palpable. No masses are felt. There is no rigidity or muscle spasm. The tendon reflexes are exaggerated.

Spinal puncture was done and 35 c.c. of fluid were removed under moderate increase in pressure. The first portion of the fluid was bloody but later became clear. A count on the fluid last obtained which was macroscopically



Fig. 1.—This shows a generally dilated aorta in walls of which are numerous foci of more severe damage at which the secondary dilatations have occurred. Multiple secondary aneurysms. One of these small aneurysms had perforated into the superior vena cava (X).



clear showed 100 cells per cubic millimeter. The urine was cloudy, yellow, contained albumin, an occasional hyaline cast, and a few pus cells. Examination of the stools for occult blood on November 29 and 30 was positive. A 24 hour specimen of urine showed specific gravity 1.005, alkaline reaction, a trace of albumin and an occasional hyaline cast. A Wassermann test on the blood was negative.

The patient became more delirious shortly after admission and remained so.

December 5 there was a purulent discharge from both eyes. The patient's condition remained much the same. On December 16 blood pressure was 100 systolic, 80 diastolic. Physical signs unaltered. He was transferred to the neurological service.

On admission the patient's temperature was 100.4°, pulse 90, respirations 22. The day after admission the temperature rose to 102.4°. Thereafter it fell to normal and remained so except for occasional rises from 99° to 100°. The pulse was between 85 and 106; respirations 20 to 24. The patient died on December 27. The day before death the temperature rose to 102.2° but fell again to 99°.

*Clinical Diagnosis.*—Delirium tremens; cirrhosis of the liver; esophageal varices.

#### AUTOPSY PROTOCOL

The body was that of a slender, emaciated man of about 40 years. The abdomen was scaphoid, the pupils were contracted, the right more than the left. About the lids there was a considerable amount of dried purulent secretion. The teeth were pigmented, the gums pyorrheic and the lips covered with sordes. The peripheral lymph glands were not enlarged and there was no peripheral edema.

When the body was opened, the lungs did not collapse though in the pleural cavities there were but a few adhesions, apical on both sides. As the bronchi were cut, a thickish, yellowish, purulent material in large amount ran from them. On both sides upon the visceral pleura over the upper lateral aspect of the lower lobes there was a scanty, thin, fibrinous exudate which was related to irregular areas of consolidation beneath. Section of the lower lobes showed an intense congestion with irregular areas of grayish consolidation. Pressure upon the tissue forced out very numerous purulent plugs from the smaller cut bronchi. The upper lobes were merely emphysematous. There was no pulmonary edema.

The liver was small, rather pale and smooth. On section, it was friable and cloudy. The lower edge lay about 1½ inches below the ensiform. It was not fibrotic.

The kidneys were small and gray. The capsules were free. The lines of demarcation between the cortices and medullæ were faint.

The spleen was small, soft, pulpy, and gray and the Malpighian corpuscles were prominent. The pancreas was healthy.

Upon the mucous membrane of the stomach there was some dark blood, mixed with a considerably increased mucus. There was no lesion from which hemorrhage appeared to have come. The esophagus was evidently healthy

and the veins not dilated. The intestines showed nothing abnormal. The bile vessels were patent.

The heart was small, very flabby and the myocardium was of a pale yellowish gray color. There were no valvular nor coronary lesions. The aorta was generally dilated in its ascending portion. The surface was wrinkled and marked by hyaline, hyperplastic patches to many of which recent red thrombi were attached. The same luetic process affected the great vessels of the neck, but not the great vessels of the abdomen.

*Anatomic Diagnosis.*—Acute purulent bronchitis; acute bronchopneumonia; luetic mesaortitis; aortic dilatation; aortic thrombi; pulmonary emphysema; acute splenitis; renal atrophy; pyorrhea alveolaris.

#### REMARKS

Because of the history of rheumatism, there may be, in this case, a suspicion of a nonluetic etiology. The anatomic evidences were typically syphilitic, and the personal history of the individual was distinctly suspicious in spite of the absence of a positive Wassermann reaction.<sup>3</sup> We know, however, that a "negative Wassermann" means very little, for Warthin has demonstrated spirochetes in the tissues of persons whose blood gave a negative Wassermann reaction.<sup>4</sup> All the facts taken collectively mean to us that the vascular condition was the result of lues.

#### CASE II

This case is one of dilatation of the aorta in which the syphilitic condition is not modified by a misleading past history or by an acute terminal condition. It is therefore consistently plainer from the standpoint of lues than Case I.

W.R., Hospital No. A-1755, a colored man, 56 years old, was admitted to the Cincinnati General Hospital on March 9, 1916. He died on March 20. On admission he complained of "stomach trouble" and "heart trouble."

The family history was negative.

*Past History.*—The patient thinks he had the ordinary diseases of childhood. At 18 he had typhoid fever. He uses whiskey and gin moderately, but gets intoxicated about twice a year. He smokes and chews tobacco excessively. He says he has had a Neisser infection three times, and, seventeen years ago, had a soft chancre. His left hip was broken many years ago; there has been some shortening.

*Present Illness.*—A year and a half ago, the present condition became apparent, when the patient noticed a precordial pain occasionally. It was apt to be present in the morning. The patient says a glass of hot water relieved him for a while, but later the pain became more or less constant. Occasionally he had spells of dizziness and shortness of breath on slight exertion. He has had considerable cough and has expectorated tenacious sputum, sometimes



Fig. 2.—An undilated aorta which at one place has been so damaged that it has bulged and formed a "saccular" aneurysm.



Fig. 3.—A sacular aneurysm in an abdominal aorta which shows no dilatation.





blood-stained. He complained of pain in his stomach after every meal; the pain lasted for a few hours and was localized in the epigastrium.

*Present State.*—The patient is a colored man of medium size, fairly well nourished. The pupils are equal and react to light and accommodation. The tongue is clean. Some teeth are missing; the remainder are carious. There is general slight glandular enlargement; the epitrochlears are palpable.

Chest expansion is small; on percussion, the note is slightly higher pitched over the left apex than the right; the percussion note over fronts and sides is otherwise good. Lower lung borders are at the fifth rib in the nipple line, equal on the two sides. On auscultation, a few crackles are heard over both fronts and sides. Voice sounds are equally transmitted. With the patient on the left side, the percussion note over the left base is higher pitched and less resonant. The breath sounds are rather weak and there are many large and small moist rales in the left base and a few scattered rales in the right base. The voice sounds are equally transmitted.

The apex of the heart is neither seen nor felt. Relative cardiac dullness extends 6 cm. to the right in the 4th intercostal space, is 16 cm. to the left in the 6th and 13.5 cm. to the left in the 4th. There is retrosternal dullness extending 2 cm. to the right and 7 cm. to the left in the 1st intercostal space. On auscultation, the sounds are best heard in the 4th intercostal space, 2 cm. within the nipple. The rhythm is regular. The sounds are fairly strong. There is gallop rhythm at the apex. A faint systolic murmur is heard at the end of the first sound; it is also audible at the base. The sounds at the base are of moderate intensity and about equal. The pulse is regular in force and the vessel walls are thickened. The blood pressure is 138 systolic, 50 diastolic. Cardiac overload is 174 per cent.

The abdomen is about level with the ribs. There is tenderness in the epigastrium. The liver and spleen are not palpable. On percussion, the liver is not below the costal margin. Knee jerks are obtained on reenforcement. The left hip is ankylosed in a valgus position. The sputum shows no tubercle bacilli. The urine is clear, acid, albumin is present, but no sugar. Microscopically, a few granular and hyaline casts, a few red cell shadows and also amorphous urates are seen. Wassermann reaction on the blood, strongly positive.

March 12. The patient has become markedly cyanotic about the face, ears, and nail beds. The heart apex is visible and just palpable 16 cm. to the left in the 6th intercostal space. The apex impulse is very weak, the cardiac dullness is the same as before; likewise the retrosternal dullness, which extends  $5\frac{1}{2}$  cm. to the left in the first intercostal space. Gallop rhythm persists at the apex. There is a very faint diastolic murmur at the apex, which becomes very distinct at the base. At the aortic and pulmonic areas there is a to-and-fro murmur. The aortic second sound is not heard.

March 14. X-ray shows the heart outline apparently enlarged to the left, extending almost to the axillary border. There also seems to be some broadening of the upper mediastinal shadow.

March 16. The patient has been expectorating bright red blood for sev-

eral days; it has become very copious today. The heart remains the same. On examination of the lungs the percussion note is hyperresonant. The breath sounds are harsh, with small moist rales scattered over all parts. No broncho-vesicular breathing is heard anywhere. Fremitus is unaltered, also vocal resonance. The expectoration of bright red blood, with the absence of signs of localized changes, makes it probable that the patient has infarcts, either too small to recognize, or not reaching the surface of the lung.

March 20. The patient has remained cyanotic. There has been gradually increasing dyspnea and weakness. Bloody sputum continues. The heart findings remain the same. The lungs remain as before, over fronts and sides. At the right base, the note is dull to above the angle of the scapula, with decrease of breath sounds. Above the dull area and over the left back the breath sounds are harsh, with many moist rales. Urine, the same as on admission. The patient died quietly at 12:30 a. m.

*Blood Examination.*—Hemoglobin, 80 per cent; red cells, 5,200,000; white blood cells, 4,000; lymphocytes 20 per cent; large mononuclears 20 per cent; transitionals 7 per cent; polynuclear neutrophils, 53 per cent; no eosinophiles or mast cells were seen in counting 200 leucocytes.

The patient's temperature was subnormal, between 95.4° and 98.4° F., from the day of admission until March 17, when the temperature rose to 100.4° F. The night of March 19, the temperature rose to 101.4° F. The pulse varied between 90 and 120; the respirations between 18 and 28.

*Clinical Summary.*—A colored male, aged 56, suffered with precordial distress, and, later, dyspnea on exertion, for one and one-half years. More recently he complained of cough and expectoration of tenacious sputum, occasionally, blood. Physical examination revealed cyanosis, dyspnea, tachycardia, subnormal temperature, great enlargement of the heart with a weak apex impulse, signs of aortic and mitral regurgitation, retrosternal dullness; there was abundant bloody sputum; the Wassermann reaction was positive; there was a marked increase in the percentage of large mononuclear leucocytes in the blood.

*Clinical Diagnosis.*—Syphilis; syphilitic mesaortitis; chronic myocarditis; hypertrophy and dilatation of the heart; dilatation of the aorta; mural cardiac (auricular) thrombi; multiple infarcts of the lungs; chronic diffuse nephritis; chronic spondylitis; ankylosis of the left hip; fluid in the pleural cavities; congestion of all viscera.

#### DISCUSSION (R. S. M.)

The marked enlargement of the heart with feeble apex impulse indicated a greatly dilated heart with probably some hypertrophy (duration of disease; cardiac overload). The mitral insufficiency was probably relative. The aortic insufficiency, associated with retrosternal dullness, a positive Wassermann reaction, and increase in the large mononuclears, make syphilitic mesaortitis altogether likely. The hemoptysis was more abundant than one usually observes with chronic passive congestion alone. Therefore, this furnished strong presumptive evidence of pulmonary infarction, even in the absence of local signs

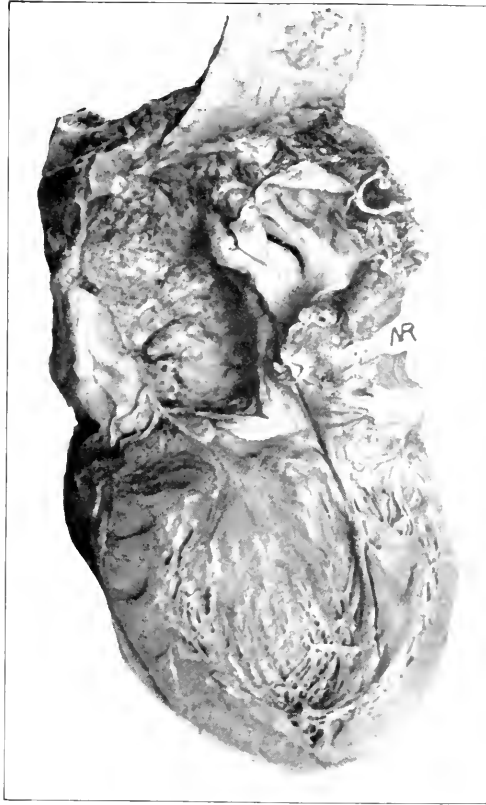


Fig. 4.—A diffusely dilated ascending arch, which has formed something between a fusiform and a saccular aneurysm.



in the lungs. If this assumption is correct, it is probable that a thrombus will be found in the right auricle, or in one of the great veins. The possibility of a weeping aneurysm as the source of the bloody sputum must be kept in mind. There was a lack of signs of localized swelling of the aorta; in fact, no evidence of a saccular aneurysm was found.

## AUTOPSY PROTOCOL

The body was that of a well built, well developed, evidently originally powerful colored man of about fifty years of age. Rigor mortis was slightly evident. Lividity was present, though not marked. The finger nails and the palms of the hands were livid. The veins of the arms were dilated. There seemed to be an ankylosis of both hips and also a general condition of ankylosis of the spine. The head moved freely upon the axis, but there was no other movement to be produced in the whole spinal column. The left leg was somewhat atrophied; the left calf and thigh were decidedly smaller than those on the right. In the abdominal cavity there was a slight increase of clear fluid. Both globi minores were enlarged and firm. The pupils were about equal, the right a little larger than the left. The conjunctivæ were slightly jaundiced. The teeth were excessively bad and showed considerable amount of caries, but the gums were apparently not pyorrhæic. The peripheral lymph glands were not appreciably enlarged. There was a considerable amount of clear dark amber-colored fluid in the right chest. There was an increase in the pericardial fluid, which was clear and dark amber. In the left pleural cavity there were about 150 c.c. of fluid. There were apical adhesions on the left side. In the right pleural cavity there were old adhesions at the apex. Over the rest of the lobe there was a recent fibrinous exudate. The intestines, aside from a slight general congestion, showed no obvious abnormality. The small intestine was contracted and the large intestine was partly dilated with gas. The peritoneum was smooth and shiny. There were no intestinal adhesions, and no evidence of inflammation. The injected, but otherwise normal, omentum was, for the most part, free, but at one corner was adherent to the parietal peritoneum and to the sigmoid at about the middle of Poupart's ligament. The appendix was *in situ* and apparently healthy. There were old adhesions between the anterior surface of the right lobe of the liver and the diaphragm.

The right lung was crepitant only in the lower lobe. The surface, except at the apex, was covered by a recent fibrinous exudate, which was easily removed. Over the middle lobe there were tags of numerous old adhesions. Almost the entire middle lobe and an area in the median diaphragmatic edge of the lower lobe were completely consolidated. There were other numerous small areas of consolidation which evidently, from appearances on the pleura, represented infarcts. The rest of the lung had a carnified feel and appearance. At the lower posterior margin of the middle lobe there was a distinct infarct. The rest of the middle lobe, however, seemed the seat of an intense congestion, massive edema and some induration. The surface of this middle lobe had somewhat the appearance of an inflammatory edema grafted upon a chronic in-

duration. The other areas of complete consolidation were evidently infarcts. The left lung was rather voluminous, the apex was torn in removing it from the body and there were a few old adhesions between the lobes. Both lobes were decidedly boggy, but had no definite circumscribed areas of consolidation. In the apex were very numerous small fibroid areas, which represented an obsolescent tuberculosis. The substance of each of the lobes was distinctly moist, quite firm, and distinctly congested. These lungs seemed to represent the lungs of a chronic passive congestion with induration and terminal edema.

The liver was of fair size, the surface was scarred on the right side by old adhesions, which occupied the gall bladder third of the right lobe. The general color of the surface was a light brownish-purple, mottled with paler areas. On cross section, the appearances were those of a typical nutmeg liver. At one point in the left lobe there was a cyst, the size of a hazelnut, filled with perfectly clear serous fluid. The friability of the liver was decreased and there was evidently a moderate amount of fibrosis secondary to the chronic passive congestion.

The heart was tremendously enlarged, both right and left. The right auricle was dilated and filled with a mass of red clotted blood. The foramen ovale was closed. The right heart was tremendously dilated and hypertrophied. The tricuspid valves seemed healthy. There were no thrombi in the auricle nor in the ventricle. The mitral orifice admitted two fingers with ease. The left auricle was not much dilated. The left ventricle was considerably dilated, so that even the hypertrophic myocardium was thin. The mitral valve was not particularly changed, but was slightly thickened at the margins of the leaflets. The chorda tendineae were somewhat sclerotic and contracted, and the papillary muscles were quite fibrotic, particularly at the tips. There was some mural fibrosis of the endocardium. The aortic valves were considerably distorted, this being particularly true of the posterior segment, which was adherent to both of the neighboring valves by old adhesions. Also this leaflet showed several fenestrations. The free margins of all the valves were thickened, rounded and sclerotic, especially at the points of union of the leaflets.

The aorta was quite badly scarred and had a puckered and hyperplastic appearance, such as goes with a luetic mesaortitis. It was dilated in its first portion above the valves, and just about 4 cm. from the innominate was a small aneurysm which just admitted the tip of the first finger. In this there were no clots. The ascending and transverse portions of the aorta, and, to a less extent, the descending, thoracic, and abdominal segments, showed well marked evidence of syphilitic aortitis, with very little calcification, a considerable amount of fatty degeneration, and, particularly in the first two parts, a very considerable amount of distortion, due to hyperplasia of the subintimal connective tissue. The myocardium, particularly that of the right ventricle, showed very decided fatty degeneration. The muscles in this cavity showed a typical thrush-breast appearance. The myocardium of the left ventricle showed very much less fatty change.

The left kidney was of about normal size and color. The capsule removed with fair ease, leaving a surface that was smooth for the most part and was



Fig. 5.—Diffuse mesoarteritis of the luteic type. Diffuse aortic dilatation. Incipient aneurysm (X). Thrombosis of innominate and carotid arteries.

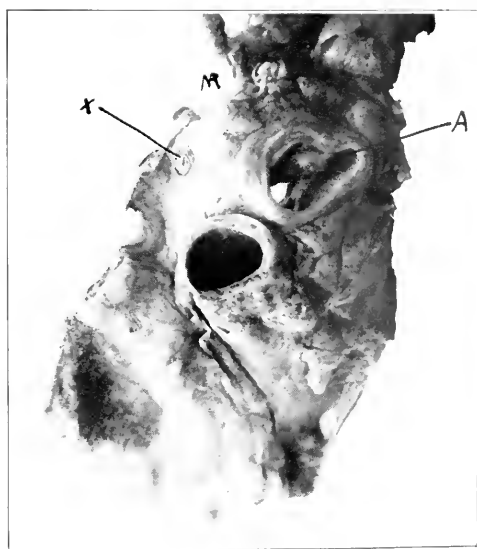


Fig. 6.—Same specimen as Fig. 5. External view, showing the trachea; partial innominate thrombosis (A), and complete carotid thrombosis (X).





nodular because of the presence of fairly numerous small, apparently infarct scars. At one point in the medulla was a small nodule, measuring about 2 mm. in diameter, of a slightly greenish-yellow color, sharply circumscribed, firm and elastic in consistence, that was possibly a gumma or a degenerated fibroma. The cortex was of normal width, and bore a normal relation to the medulla; the line of demarcation was distinct between cortex and medulla, the stellate veins were not congested. The friability of the organ did not seem to be increased and there was no distinct evidence of fibrosis. The right kidney was slightly larger than the left, and had the same general appearance, except for the presence of the small nodule that appeared in the left. The adrenals showed no gross abnormality. There was nothing obviously abnormal to be seen in either testicles or epididymis. Both the latter were, however, apparently sclerotic and quite firm to the feel.

The spleen was small, quite firm, and had a somewhat nodular surface. There were no evidences of infarcts. On cross section, the pulp was dark red in color, quite firm, and the organ was apparently somewhat fibrotic. The Malpighian bodies were just visible.

The pancreas was rather firm, evidently congested, but showed no other macroscopic lesion.

The stomach was diffusely reddened and showed a small number of fine hemorrhages. There was an increase of mucus on the surface. The rugæ disappeared almost completely on stretching the organ. The duodenum was also diffusely congested and showed an increase of mucus.

The whole intestinal tract was deeply congested, and had a slightly increased amount of mucous material over the surface.

*Anatomic Diagnosis.*—Syphilitic mesaortitis; dilatation of the aorta; aortic aneurysm; chronic sclerotic aortic valvular endocarditis; hypertrophy and dilatation of the heart; fatty degeneration of the myocardium; pleural and pericardial effusions; acute fibrinous pleuritis; pulmonary infarcts; chronic passive congestion of the thoracic and abdominal organs; gumma of the kidney (?); spondylitis deformans; bilateral-ankylosis of the hips.

#### REMARKS

The protocol shows how well justified the clinical diagnosis was. As had been suspected, the case was essentially a cardiovascular complex, the result of syphilitic infection. This infection showed its main effects in the arteries, reduced their elasticity and threw an ever-increasing burden upon the heart which had accommodated itself as long as it was able, and then, having undergone a compensatory hypertrophy, failed and dilated. The vascular burden was not the only thing which affected the heart. The aortic valves, the seat of a luetic process, became damaged and incompetent. The aorta, severely affected, could not resist the internal pressure and not only dilated

generally, especially in the ascending arch, but also locally, in the same segment, as was shown by the small aneurysm.

During the development of the cardiac condition, the lungs became the seat of a passive congestion due to relative mitral insufficiency, and then being less resistant to infection, an inflammatory process developed which had not progressed to the formation of a pneumonia at the time of death, but which appeared only as an inflammatory edema associated with an acute pleuritis. The lack of pulmonary ventilation plus the terminal intoxication led to the fatty degeneration of the myocardium, and it was probably this which was the last straw. The infarcts were probably marantic, due to clotting of the blood in the right auricle before death.

### CASE III

This case illustrates the anatomic condition known as fusiform aneurysm, which differs from dilatation of the aorta only in the fact that the area of transition from diseased to healthy aorta is more limited, so that, instead of very gradually departing from its normal caliber, the vessel becomes dilated somewhat rapidly, and as rapidly becomes reduced again at its distal part. As a matter of fact it seems that the distinction between aortic dilatation and fusiform aneurysm is unnecessary.

M. H., Hospital No. A-4572, a married negress, 38 years old, was admitted to the Cincinnati Hospital on July 5, 1916. She died on July 14. She had been in the hospital three times before with the same symptoms, of which she complained at this admission; namely, pain, dyspnea and brassy cough. On her previous admission numerous x-rays were made all of which showed a distinct broadening of the upper mediastinal shadow, which was interpreted as indicative of an aneurysm of the aortic arch. At the time of the last admission she had a typical "goose cough," was dyspneic, and had pain in and about the right shoulder. All of these symptoms were more marked than at the time of her last discharge.

The following notes on physical examination were made: "The patient shows extreme respiratory distress, and 'goose cough.' There is evidence of increased broadening of the mediastinum, especially to the right. There is a fullness in the jugulars and jugular pulsation. The heart sounds are very clearly heard over the area of cardiac dullness. The apex beat is not palpable. There is no evidence of cardiac transposition. The heart sounds are very rapid and weak. Dyspnea is inspiratory. Over the anterior chest sibilant rales are heard. The breath sounds over the trachea are not altered speaking against dyspnea of tracheal origin. There is not edema. There is a paretic condition of the right arm and hand. The temperature was irregular and not accounted for." There were no further notes.

During her stay in the hospital, the patient's temperature varied between



Fig. 7.—An aorta the seat of a diffuse luetic process. At one place that wall has become more weakened and at the point a sacular aneurysm has been formed. It is filled with clot.



98° and 103.4°; the pulso between 90 and 160(?); respiration between 18 and 36. There was no note of urinary examination, blood pressure, or blood count.

*Clinical Diagnosis.*—Aortic aneurysm (?). Mediastinal tumor (?).

#### AUTOPSY PROTOCOL (M)

The body was that of a well developed, well nourished negro woman about 45 years of age. The pupils were dilated and equal and an arcus senilis was present in each cornea. Most of the upper teeth were missing. The upper left canine and also one of the incisors contained a large cavity. The gums were retracted. The superficial veins of the upper extremities and the upper portion of the chest were somewhat dilated. Over the buttocks there was a superficial excoriation. Hemorrhoids were present. The superficial fat was quite large in amount and of good color. The appendix remained as a fibrous cord and was very slightly congested in its tip. The lower border of the liver extended  $8\frac{1}{2}$  cm. below the tip of the ensiform cartilage.

When the sternum was removed, there was found just behind and slightly adherent to it a large mass filling the entire mediastinal cavity. A few apical adhesions were present on the left lung. The right lung was bound laterally by rather dense adhesions and was also adherent to the mediastinal mass at the lower edge of its anterior margin. This mass was adherent to the clavicle of the first rib. The structures of the thorax, neck, and mouth were removed. The liver was adherent along its upper border by rather recent fibrous adhesions to the diaphragm.

The right lung was somewhat small and had upon its surface the tags of old adhesions. The lobes were bound together by rather dense adhesions. The organ was crepitant throughout. The cut surface of the upper lobe showed nothing abnormal except a moderate edema and some congestion; in the anterior portion of the lower lobe there was an area which was rather denser than usual which did not crepitate and which on section showed a great degree of congestion and some edema. In the apex of the upper lobe of the left lung and also in the lower lobe could be felt a number of rather small hardened areas which on section proved to be healed tubercles. The vocal cords seemed to be healthy. Beneath the vocal cords at the first cartilage there was a small area measuring about 3 by 5 mm. in diameter, that was of a bluish-red color and seemed to be a hemorrhagic area. Just at the point of bifurcation of the trachea and extending upward for a distance of 3 cm., there was a raised area that was gelatinous in appearance, the base of which was injected and which felt rather soft. The trachea at this point was very greatly injected.

The right auricle and ventricle were both somewhat contracted. The tricuspid valves, other than a slight thickening along the free edges, were healthy. In the wall of the left ventricle there was an area, measuring about 3.5 by 0.5 cm. which contained a great deal of fat. The valves were all apparently healthy throughout. The aorta, beginning at the origin and extending forward and through its transverse portion was tremendously dilated and in portions was sacculated. This dilatation was filled with a well-or-

ganized clot, which was readily removed. This aneurysm, in the region of the bifurcation of the trachea, had begun to press forward upon the trachea but had not extended into it. The dilatation was greater than that of an ordinary official baseball. The aorta contained in its extent a number of fatty plaques and also many areas of hyaline degeneration, luetic in type. The heart muscle contained some fibrous tissue.

The liver was slightly decreased in size and showed upon its surface the remains of fibrous tags. The surface was of a mottled reddish-blue color. The organ cut with some increased resistance and was firmer than usual. The cut surface was yellowish in which there were mottled areas of reddish-blue and had the typical appearance of chronic passive congestion. The gall ducts were patent and there were no stones.

The kidneys were of about normal size and of a bluish-red color. The capsules stripped very easily, leaving smooth surfaces upon which the stellate veins were much congested. The cut surfaces were rather pale in appearance. The cortices were of about normal thickness and the lines of demarcation between cortex and medulla were rather indistinct. The glomeruli were visible as red congested points. The organs were edematous.

The spleen was of normal size and on cut section showed nothing unusual.

The ovaries and tubes were apparently healthy. The cervix was small and firm and from it issued an extremely gelatinous material. The uterus was very small and beneath the endometrium was a small round fibroid. Scattered throughout the musculature also were other small fibroids. There was a moderate congestion of the trigone at the neck of the bladder.

*Anatomic Diagnosis.*—Fusiform aneurysm of the aorta; syphilitic aortitis; acute catarrhal tracheitis; chronic passive congestion of the liver, spleen, and kidneys; obsolescent pulmonary tuberculosis.

#### REMARKS

The appearances in this case suggest that the aorta was so diffusely damaged by the infectious process that it became, at least in one complete section, dilated, and assumed a fusiform shape. They also suggest that in the wall of the aneurysm there were points of greater damage so that small secondary aneurysms were incipient. Evidently also there was some pressure upon the trachea producing irritation and accounting for the cough.

#### CASE IV

This case represents the extreme of aortic dilatation for in it the whole vessel was affected.

W. H., Hospital No. A-2275, a married white man, 47 years old and a laborer, was admitted to the Cincinnati General Hospital on March 29, 1916. He died April 11. He complained of "shortness of breath, pains in the chest, back, and over the kidneys."

The family history was negative.

*Past History.*—The patient had the ordinary diseases of childhood, including diphtheria. He had "typhoid" and "malaria" several years ago. At 19 he had inflammatory rheumatism. About 3 years ago he noticed shooting pains about the heart accompanied by shortness of breath. He rested a few weeks and improved so that he was able to return to work.

*Present Illness.*—A week before Christmas the patient was taken with pain about his heart and shortness of breath. He rested somewhat at home, but failed to improve satisfactorily. For the past few weeks he has complained of slight swelling of the feet.

The following notes are quoted verbatim from the clinical history. They are quoted with regret. The case is used because of the interest attached to the anatomic condition.

*Present State.*—"Patient was emaciated and anemic and slightly cyanotic. Conjunctiva negative. Teeth are poor. Some pyorrhea. Glands not palpable. The heart is dilated and displaced toward the axilla and downward. Double bruit heard at base. Systolic at apex. Sounds not strong. Pulses are weak. Lungs seem filled at the bases with fluid. Patient is expectorating some blood. Large mucous rales heard all over chest. Liver is enlarged. Not hard and smooth. No jaundice. No fluid in lungs. Extremities somewhat edematous. Urine contained albumin, but no sugar. Blood was present.

"Patient's condition got progressively worse. Dyspnea and cyanosis increased. Lungs finally became filled until tracheal rales were pronounced. Patient expectorated large quantity of blood. Passed into coma after a few hours of subconscientness, and died April 11, 7 a. m."

Patient was admitted with subnormal temperature. This rose from 100° on April 7, to 102°, from 96.4° to 102° on April 9, and on April 10 it was between 100.2° and 102.6°. Pulse was between 100 and 120. Respirations 24 to 36.

*Clinical Diagnosis.*—Mitral regurgitation; aortic regurgitation; passive congestion of the liver and portal system; congestion of the lungs.

#### AUTOPSY PROTOCOL

The body of a well built, fairly well nourished white man of about 45 to 50 years of age. There was a very well marked edema of both legs and of the penis. The peripheral lymph glands were perceptibly enlarged and firm. Just beneath the chin was the scar of a transverse incision which was almost covered with gray beard. The teeth were mostly in a fairly good condition. They were worn down and, particularly in the upper jaw, there were three or four that were carious. The pupils were equal; the conjunctivæ were pale. Rigor mortis was absent. Postmortem lividity was present. The body was still warm. There was a more or less general edema of the body, which was particularly marked in the posterior parts. The veins of the neck were dilated. The face was livid. The lips were fissured. The finger nails were slightly livid, although the whole body was distinctly pale. Scattered more or less indiscriminately over the body, always in positions that could be

reached by the fingers, were scratch marks which indicated an ectozoic infection.

The subcutaneous fat was fairly well developed and slightly edematous. The muscles were well developed and of good color and were also slightly edematous. The intestines lay in their normal positions. The appendix was *in situ*, lying behind the cecum, bound down by old adhesions, and was about 1½ inches in length. The peritoneal surface of the intestines was smooth and shining. There were no evidences of inflammation. Occasionally one of the loops appeared to have a somewhat darker color than the others and this color suggested the presence of blood within the loop. The stomach was moderately dilated in the cardiac portion, contracted in the pyloric.

When the thorax was opened, the lungs did not collapse. The right pleural cavity was almost completely filled with a turbid brownish fluid containing large floccules of fibrin. There was no fluid in the left pleural cavity. There was a moderate increase in fluid in the pericardial cavity and this fluid was for the most part clear but contained some floccules of fibrin and had a yellowish amber color. There were no adhesions in either pleural cavity. The omentum was coiled up above the transverse colon, was fairly well supplied with fat and distinctly edematous. In the lower part of the sigmoid were series of diverticula containing fecal concretions. Part of the omentum was turned up over the spleen to which it was adherent over the whole splenic surface. The portal vein was dilated.

The right lung was rather voluminous. The upper and middle lobes were completely crepitant although they were somewhat boggy. The lower lobe was only partially crepitant, the consolidated area being present posterolaterally and involving the diaphragmatic surface. The surface was injected and covered with a thin fibrinous membrane. The surface of the consolidated area was raised above the surroundings. The pleura about this area, in the crepitant parts, was injected and covered with fine ecchymotic patches. On section, the upper and middle lobes were moist but not edematous. There were no areas of consolidation within the substance. The lower lobe was very deeply congested in the consolidated portion, but the congestion was not well localized, but was rather diffuse. There was no distinct line of demarcation about this area. In a vessel supplying it there was, however, a very distinct thrombus which completely filled the vessel. The rest of the lobe was merely congested. The left lung was completely crepitant in the upper lobe; the lower lobe was almost completely noncrepitant. The only air-containing portion was the upper portion of the lobe. The pleura of the upper lobe showed a couple of well defined stellate scars in the thickened pleura. The lower lobe was not only consolidated, but had the feel of being quite soft, as though the tissue had been broken down. Over these apparently softened areas there was a gangrening of the pleura. Upon the rest of the pleura of this lobe there was a distinctly fibrinous exudate. Section of the lower lobe showed a perfectly tremendous state of congestion and upon opening this area it had the appearance of being softened and had a tremendously foul odor. The blood vessels leading to this area were, as in the case of the other lung, thrombosed.



The heart was exceedingly large—at least twice as large as it should be. In the pericardium there were large numbers of discrete and confluent hemorrhages, and in the epicardium, particularly over the base, there were quite numerous small ecchymotic hemorrhages. The pericardium over the right auricle was thickened. In the right auricle, particularly in the auricular appendage was a quite adherent mixed clot. The subepicardial fat was gelatinous. In the left auricle there were a few well formed mural thrombi between the muscle columns. The mitral orifice admitted the tips of three fingers—two and a half with ease. The aortic orifice admitted the tips of two fingers. All of the cavities of the heart were dilated and the myocardium was generally hypertrophied and distinctly pale and distinctly and generally fibrotic. This was particularly true of the papillary muscles which were composed of fully as much fibrous tissue as muscle tissue. There were occasional patches that could be seen, particularly over the endocardium of the left side that gave evidence of fatty degeneration. The leaflets of the valves themselves were not particularly abnormal. The mitral leaflets were somewhat thickened at the margins, the tendons were somewhat contracted, but nothing else. The tricuspid orifice, though dilated, showed no other abnormality; the same was true of the pulmonary. The aortic orifice was dilated but the valves themselves were not particularly changed. They were slightly thickened at the margins, a little adherent at the points of insertion, but otherwise showed nothing unusual.

The aorta was tremendously and almost diffusely dilated, though the dilatation was best shown in the ascending arch where the wall was not only diffusely calcified but was also diffusely thin and the seat of very many atheromatous ulcers and abscesses. The condition was that of a diffuse aneurysm of the ascending arch and this dilatation involved also the innominate artery. Beyond the arch there was also a certain amount of dilatation and the aortic process extended diffusely down into the femorals and iliacs. In the thoracic aorta, about 3 inches from the subclavian, was a slight dilatation that just admitted the tip of the first finger, that seemed to represent the beginning of an aneurysm. The walls of this were completely calcified.

The spleen was of about normal weight. It was tagged with the remains of old fibrous adhesions. It was of a rather dark purple color. The pulp was firm, but very rich in blood. There was a moderate increase in fibrous tissue. The Malpighian bodies were not visible. The veins were dilated.

The liver was small and quite firm. The smooth surface had rather a granular appearance, as though there were an increased amount of connective tissue within the organ. The general color was pale but mottled with lobular markings of congestion. At one place on the dome, there was a small gray area which measured about 2 mm. in diameter, which was rather firm, elastic, had a yellow center, and was rather well circumscribed and possibly represented a gumma. On section, the liver had the typical nutmeg appearance. The veins were dilated and the resistance to cutting was increased. There were a few other areas that may have possibly represented an early stage of gumma formation.

The right adrenal was a trifle small if anything, but otherwise showed nothing unusual except possibly an increase in the lipid content of the cortex. The right kidney was a trifle smaller than normal and rather congested. The cortex removed with comparative ease, although it tore the surface at a few points. Scattered upon the surface were small, rather irregular, but well organized, areas of rather deeper color than the rest of the organ, that seemed to be surrounded by a zone of congestion. These areas extended into the kidney substance in the form of wedges. They were evidently very recent red infarcts. The cortex was narrow, the line of demarcation between cortex and medulla was faint, but the whole parenchyma was congested and evidently fibroid. The fibrosis showed, macroscopically, best in the papillæ. The glomeruli could just been seen as fine congested points. The left adrenal showed nothing unusual. The left kidney was similar to the right.

The bladder was filled with a clear amber-colored urine. The mucous membrane was apparently healthy. The prostate was perhaps slightly enlarged and about it the venous plexus was distinctly congested. The substance of the prostate showed nothing unusual.

The stomach was generally congested and showed the beginnings of slaty pigmentation. The congestion was best shown on the tops of the rugæ and the rugæ were with difficulty flattened upon stretching. Between the rugæ there was an increased amount of greenish-stained mucus. Also the mucous membrane had a distinct morocco-leather appearance. The duodenum, except for a moderate congestion and an increase in mucus upon the surface, was apparently healthy.

The pancreas was quite firm, possibly somewhat fibroid and showed no gross abnormality. The splenic artery was moderately sclerosed but not excessively so. There was only a moderate degree of sclerosis of the other branches of the celiac axis.

Within the small intestine, particularly in the jejunum in its lower portion, and to a lesser extent in the ileum, there was a considerable amount of blood pigment adherent to the rugæ. The rest of the intestine was generally congested and upon the surface there was an increase in mucous secretion. The lymphoid follicles were not hyperplastic. The large intestine particularly was congested. At several points there were small openings which led through the mucosa into the diverticula mentioned earlier in the protocol.

*Anatomic Diagnosis.*—Syphilitic aortitis; diffuse dilatation of the aorta; hypertrophy and dilatation of the heart; myocardial fibrosis; auricular cardiac thrombi; pulmonary and renal infarcts; pulmonary gangrene; acute fibrinous pleuritis; chronic passive congestion of the thoracic and abdominal viscera; chronic catarrhal gastritis; multiple diverticula of the sigmoid and rectum; gumma of the liver.

#### REMARKS

The evidences of lues, and the part played by it in this case are reinforced by the presence of an hepatic gumma. The syphilis was evidently exceedingly diffuse and had affected the whole cardiovascu-

lar system severely. Not only was the aorta damaged so that it could not withstand the pressure, but the heart also was so damaged that after it had done its best and hypertrophied, it too dilated, and, the blood flow becoming slow, auricular thrombi were formed in both auricular appendages. These accounted for the infarcts. The pleurisy was evidently the result of the infarction and the coincidental inflammatory reaction.

#### CASE V

This case illustrates the results of a severe lues in which the aorta was very seriously and diffusely damaged, especially at one point where an aneurysm was incipient.

W. H., Hospital No. A-1368, a colored man, 27 years old, was admitted to the Cincinnati General Hospital on February 24, 1916. He died two hours after admission.

*Complaint.*—"Pain in the heart, and swelling of the legs."

The family history was unimportant.

*Past History.*—He had been strong and while a child had had only measles and mumps. At the age of 18, he had a chancre and at 22, had had gonorrhea. He said he had "rheumatism" once. He used alcohol and tobacco to excess.

*Present Illness.*—The onset of the present illness occurred nine months before admission, and was characterized by shortness of breath on exertion. Later he became dyspneic without exertion and had dizzy spells. A few months after the onset he noticed a sharp pain in the region of the heart. This appeared after the least exertion. He became exceedingly weak, and about 3 weeks before admission his legs began to swell. He kept growing gradually worse.

*Present State.*—"The patient is a fairly well nourished man. The pupils react to light and during accommodation. The conjunctivæ are injected. The anterior and posterior cervical glands are palpable; the tongue is clean; the teeth in poor condition; the chest fairly well nourished. Over the upper part of the right lung the percussion note is resonant, but below it is impaired, and there are large wheezing expiratory rales and many small dry rales. The breath sounds are roughened throughout. Over the left lung the percussion note is resonant above, impaired below. The same auscultatory signs, as on the right, are present. The cardiac apex impulse is in the 6th space in the midclavicular line and is diffuse. The rhythm is fair. There is a systolic and a doubtful diastolic murmur. The first sound is muffled and accentuated. The pulse is weak. The abdomen is distended. There is rigidity. Knee jerks were not obtained. Specific scars are present in legs, chest and back."

The temperature was 100° on admission and rose to 103°. The pulse was 104, rising to 134. No urinary or blood examinations were given.

*Clinical Diagnosis.*—Mitral regurgitation; chronic interstitial nephritis; general anasarca.

## AUTOPSY PROTOCOL

The body was that of a well built, well nourished, colored man. The legs were exceedingly edematous; as a matter of fact, the whole body was edematous. The eyes were prominent, almost protruding between the lids. The pupils were equal. The teeth were in fairly good condition. The two upper middle incisors were missing. The finger nails were cyanotic. Rigor mortis was present to a moderate extent in the legs, practically absent in the arms. The abdomen was bulging and seemed to contain fluid. On the thorax, about the midmammary line, were numbers of small cutaneous hemorrhagic papular lesions measuring not more than two millimeters in diameter. There were a few similar papules on the arms and on the face. On the forehead, above the right eye, was a scar running directly toward the occiput, 8 cm. long.

The abdomen contained a couple of liters of a somewhat cloudy, yellowish, serous fluid. The subcutaneous tissues and muscles were water-logged. The lower border of the liver was 9 cm. below the tip of the ensiform. The stomach was somewhat distended with gas. The appendix was present, kinked beneath the caput coli. Otherwise there was nothing abnormal to be seen in the peritoneal cavity. The stomach had an incomplete hourglass shape.

When the sternum was removed, the lungs did not collapse. In the left pleural cavity there were old diaphragmatic adhesions and a small amount (200 c.c.), of a serous fluid. The right pleural cavity was perfectly obliterated by old adhesions. These adhesions were filled with edema fluid and were gelatinous in appearance. The bronchi were intensely congested. The pericardium contained an increased amount of a yellowish fluid.

The mesentery was edematous and congested. Throughout the mesentery there were very large numbers of exceedingly fine hemorrhages.

The heart was exceedingly large. The surface showed brilliant capillary congestion and at the base, particularly over the left ventricle, were masses of fine hemorrhages under the epicardium and also in the pericardium. The right auricle was dilated and filled with a mass of red clot. The tricuspid and pulmonary valves seemed to be healthy. Neither of the auricular appendages contained thrombi. The mitral orifice barely admitted the tips of two fingers. The aortic orifice was narrow. The left ventricle was very much dilated. The mitral valve was quite sclerotic and very much thickened. This fibrosis included not only the valves, but also the tendons connecting the valves with the papillary muscles which were composed entirely of fibrous tissue and were thickened and contracted. The papillary muscles themselves were quite fibrotic. The aortic leaflets, especially the posterior and right ones, were almost completely destroyed by a chronic ulcerative and fibrotic process. The points of attachment of these valves had completely disappeared and occupying the place at which the attachment should have been, was a mass of organized vegetations the size of a split pea. These two valves, together, formed a sort of thickened, almost cartilaginous, semicircle. The left valve was sclerosed and contracted. The myocardium was generally fibrotic. The columnæ carneæ were hypertrophied and gave a well marked trabeculated appearance to the cavities. Commencing above the aortic valves, and reaching

through the transverse portion of the arch, the surface of the aorta was tremendously distorted with large and small plaques, in some of which apparently was calcification with numerous areas of fatty degeneration, and in some areas of which there was considerable atheromatous degeneration. Just to the right of the innominate artery was a large plaque, 4 cm. in diameter, which represented an incomplete aneurysm. The wall of this area was hyaline in appearance, the hyaline being rather irregularly distributed. The wall of the aorta was exceedingly thick and fibrotic. In the descending arch and the abdominal aorta, there was nothing more than rather diffusely scattered patches of fatty degeneration.

The left lung was voluminous and soggy. Upon the pleura, particularly laterally over the upper lobe, were numerous small pleural hemorrhages, while the whole lung was crepitant, nevertheless the areas of crepitation were scattered. On section, the tissue appeared tremendously edematous and congested, rather semisolid to the feel, as though incompletely consolidated. All of the tissues, however, were air-containing, and even small pieces of the tissue floated in water. The right lung was distorted because of old pleural adhesions. On section, however, the tissue had the same appearances as the left—showed a tremendous edema associated with congestion.

The liver was rather decreased in size, the surface was smooth, so far as adhesions were concerned, but there were a few scattered areas of capsular thickening, some of which had stellate appearances, but none of which projected into the tissue. The general color was a pale, washed-out purple mottled with yellow. On cross section, the liver had a typical nutmeg appearance of chronic passive congestion in an advanced stage. Decreased friability and a somewhat lobular feeling of the organ indicated a considerable increase in fibrous tissue.

The stomach was tremendously congested, and in the mucous membrane were very numerous scattered small hemorrhages. The duodenum showed the same appearances. The bile ducts were patent.

The pancreas showed only a well marked congestion.

The spleen was exceedingly small and firm. The capsule was slightly thickened, in some areas the general color was a distinct bluish-purple. The pulp was very firm and deep red in color. The Malpighian bodies were not visible, but there was a visible increase in fibrous tissue. There was considerable congestion.

The right kidney was of about normal size, (160 grams), was exceedingly firm and elastic. On cross section it showed a well marked edema of the pelvic tissue. The capsule stripped with comparative ease, leaving a surface which was for the most part smooth and untorn, but at some points somewhat granular. The cortex was of normal thickness, the line of demarcation between cortex and medulla was brilliant. There was evidence of some sclerosis in the pyramids. The friability of the organ was decreased. The glomeruli could be seen as pale shining points. The whole organ was paler in color than normal and there were occasional scars of old infarcts. The left kidney

(150 grams) showed practically the same appearances. The capsule, however, was rather more adherent and there were more infarct scars.

The upper part of the rectum was edematous; the mucous membrane was covered with a quite tenacious, somewhat adherent, mucous covering, beneath which the mucous membrane was not ulcerated. This acute catarrhal condition extended throughout the whole large intestine and was even more marked in the ascending colon, where it was associated with more congestion. It was present also, to a less degree, throughout the small intestine. In the jejunum, especially in the upper part, there was a very well marked degree of congestion and less edema.

*Anatomic Diagnosis.*—Chronic ulcerative aortic endocarditis; chronic mitral endocarditis; mitral stenosis; syphilitic mesoarteritis; incomplete aortic aneurysm; chronic diffuse (parenchymatous) nephritis; chronic passive congestion of lungs, liver, kidneys, spleen, pancreas, stomach and intestines; edema of lungs, acute membranous colitis; acute catarrhal enterocolitis.

#### REMARKS

In this case the luetic process was most evident in the aortic valvular segment and, therefore, may be called ulcerative only in the sense that the ulcers were of the atheromatous type. The mitral lesion also was of the sclerotic type which Huchard associated with general arteriosclerosis, gout and lead poisoning, and which others, among them Goodhart, associated also with anemia and chronic overstrain.<sup>5</sup> Whether it may have been a true sequel of the lues, can not be said. It is possible that the fibrosis of papillary muscles consequent upon the syphilis was followed by changes in the chordæ and that this became the cause of the valvular lesion. However that may be, the coincidence of the two lesions is disturbing because lues is not commonly associated with mitral lesions. Concerning the aorta itself there can be no doubt of the specific etiology.

#### CASE VI

This case illustrates what may happen when even a small area of the aortic wall is sufficiently weakened.

J. B., Hospital No. A-7856, a colored male, aged 51, a farmer, was admitted to the Cincinnati General Hospital, November 27, 1916, complaining of "pain in the right side and shortness of breath."

The family history is unimportant.

*Past History.*—The patient had measles, mumps, and chicken pox in childhood. Also has had typhoid fever and several attacks of malaria. Otherwise his health has been good. Says he has had gonorrhea and syphilis.

*Present Illness.*—The present trouble began November 25, with pain in the right side. Sunday night he had frequent chills of short duration.

*Physical Examination.*—The pupils react to light and accommodation. The tongue is coated. The teeth are in poor shape. There is pyorrhea alveolaris. Both apices are dull on percussion. At the left base there is a friction rub and resonating rales with relative dullness. There is roughened breathing all over. The heart is normal. The abdomen and extremities are negative on examination.

The patient was having a chill on admission. Temperature 97°, pulse 96, respirations 20. The patient has expectorated blood and has had severe night sweats.

November 29. There is a friction rub over both bases, and rigidity and tenderness over the left abdomen. The pain is cramp-like in character and does not radiate. No nausea, vomiting or jaundice.

November 30. There is rigidity of the abdomen, distention and a small amount of fluid in the abdomen. Tenderness over McBurney's point. Leucocytes 12,600. No differential count made. There is no vomiting though the patient is slightly nauseated. Rigidity and tenderness increasing. Sudden drop in temperature to 93°, pulse 112, irregular and thready. Surgical interference was advised against on account of the patient's general condition. The patient has begun to hiccup. An inflammatory mass fills the pelvis and is palpated per rectum.

November 29. X-ray examination of the chest showed an accentuation of the normal markings radiating from the hilum of each side with some nodular thickenings along them suggesting thickenings along the bronchial tree. There is a shadow bulging into the left chest with semicircular contours which suggests either an aneurysm, dilatation, or large gland. From the character of the density of this shadow it resembles a large glandular mass rather than an aneurysm.

*Summary.*—The patient had intermittent fever and abdominal pain, tenderness and rigidity. The minimal temperature was 95°, maximal 101.4°, pulse 92 to 144, respirations 18 to 28. Wassermann blood test was positive. Two sputum examinations failed to reveal tubercle bacilli.

The patient died December 1.

*Clinical Diagnosis.*—Pulmonary tuberculosis; fibrinous pleurisy; chronic myocarditis; acute peritonitis; ruptured appendix (?); atheroma of the aorta; lues.

#### AUTOPSY PROTOCOL

The body was that of a tall slenderly built negro apparently about 50 years of age. Rigor mortis was present; postmortem lividity was also present. Extending immediately over the vertex from ear to ear was the scar of an old incision. The peripheral lymph glands were not visibly enlarged. There was no edema of the legs. The omentum was infiltrated with pus and formed a thin apron reaching down into the right inguinal region in which there was a large amount of rather dry adherent fibrinous membrane. Throughout the abdominal cavity there was a considerable amount of the same sort of fibrinous exudate. The inflammatory process was accentuated in the appendix region where there was a large collection of pus infiltrating the psoas

muscle and anterior extraperitoneal tissue. The appendix itself was *in situ* and was surrounded by and embedded in pus, but did not seem to be the source of the peritonitis. Its walls were intact and it was not inflamed except externally. Running up behind the ascending colon, the exudate was more remarkable in quantity. The anterior mediastinal lymph glands were very hyperplastic, succulent and congested. On section they showed no evidence of anything except acute congestion. When the intestines were dissected it seemed that the massing of the inflammatory process and of the pus was behind the ascending colon anterior to the right kidney.

In the left pleural cavity were a few old apical adhesions and there were also more numerous diaphragmatic ones. In the right pleural cavity were only diaphragmatic adhesions both old and recent. There was an encapsulated empyema between the diaphragm and the lower lobe. The duodenum was practically buried in pus and surrounded by old and recent adhesions.

The mass which seemed to be composed of the right kidney was at least twice the size of a normal kidney. On section, this mass appeared to be composed of several cystic spaces containing a grumous material with a good deal of pus. The rest of the substance of this mass was composed of infiltrated fat. There was no visible evidence of any functioning kidney substance in the mass. The left kidney was larger than normal and contained cystic spaces filled with necrotic-looking material containing some pus. There was no line of demarcation between cortex and medulla. Many of the pyramids seemed to have been completely replaced by cystic spaces. The whole cortical material was exceedingly gray. The interlobular vessels showed very well but the glomeruli were not visible. The pelvis seemed not to be particularly changed except just at the calices where it was thickened and pigmented. On dissection it appeared that most of these cystic-looking spaces were in reality dilated calices in which there was a well marked inflammatory process. At numerous places there were patches of fibrous membrane upon the surface of the cystic spaces. Except at the points of contraction and degeneration of the kidney substance, the capsule removed with fair ease.

The heart was small and flabby and the right auricle particularly was dilated. The right ventricle was less dilated. There was no valvular lesion on the right side of the heart. The myocardium was firm and brown and evidently fibrotic. The papillary muscles, particularly, were sclerosed. The aorta itself, particularly the descending portion, was the seat of a very well marked luetic process which was present to a less extent in the ascending and transverse portions. Just at the upper and posterior part of the descending arch was an opening in the wall of the aorta which measured 19 by 22 mm. in diameter. This led into a sac which was almost completely round and about 5.5 cm. in diameter, which was completely filled with clot. The center of the clot was evidently undergoing softening.

The liver was of normal size but the whole surface was tagged with recent and old adhesions and the surface was irregularly contracted by old, more or less stellate scars diffusely scattered. Resistance to cutting was increased and throughout the organ could be seen an increased amount of fibrous tis-



sue. The gall bladder contained a fair amount of rather dark brown mucoid bile and no stones and no sand.

The left lung was crepitant throughout except for an area occupying the anterior triangle of the lower lobe at which point the lung was completely consolidated. Over it there was no evidence of recent inflammatory process. On section of this part of the lung, one discovered a collection of abscesses the largest of which was 1 cm. in diameter. Each of these was surrounded by a well marked zone of congestion and the smaller ones were filled with a rather creamy pus, the larger with a material that seemed almost typically caseous. The right lung was rather more voluminous than the left, more edematous and, except for an area in the lower lobe postero-medially, was crepitant. This area of consolidation had practically the same appearance as that of the other lobe except that in it there was a more marked congestion.

The spleen was very small, the capsule thickened and tagged with old adhesions. The substance was pale and fibrotic. The Malpighian bodies were not visible and the fibrous tissue was increased.

The stomach showed nothing unusual. The whole gastrointestinal tract was somewhat edematous and in some areas showed a moderate congestion but there was no anatomic lesion of note.

The brain showed nothing unusual.

*Anatomic Diagnosis.*—General fibrino-purulent peritonitis; perirenal abscess; diaphragmatic empyema; pulmonary abscesses; suppurative nephritis; luetic mesaortitis; aortic aneurysm; myocardial fibrosis.

#### REMARKS

For the purpose of the present discussion the peritonitis is not essential. It evidently originated in the kidney whence it invaded the peritoneum. The point here is that the aorta, though rather diffusely affected by a syphilitic infection, was more deeply damaged at one small area, and it was this area which, affected by the intravascular pressure, gave way and bulged. In this case the Wassermann reaction was positive and, therefore, there is no doubt, in spite of the man's age, of the specificity of the arterial lesions.

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# SEROLOGICAL EXAMINATION OF OVER TWO HUNDRED CHILDREN FROM THE OPEN AIR SCHOOLS OF ST. LOUIS

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THE authorities having charge of the children in the open air schools of the city of St. Louis asked, with the full consent of the Department of Hygiene of the Board of Education, that certain examinations be made of the children attending these schools at the Dispensary of the St. Louis University School of Medicine.

The serum diagnosis for syphilis has been applied routinely in all departments of medicine, and to practically every class of individuals that might be conveniently grouped in any manner. The children of these open air schools constitute a special group probably not comparable to any other group taken at random in the city of St. Louis, or possibly even not comparable to a group selected upon a similar basis in any other city.

These open air schools were arranged for children suffering from anemia and malnutrition of apparently unknown origin. The general impression was that these schools were maintained for the tuberculous and those of a tuberculous diathesis, and in the earlier periods when these schools were first opened some of the school medical inspectors selected only those of a tuberculous diathesis. A few cases with a definite heart lesion were also admitted. Later it became the policy to exclude cases with definite lesions of any kind, and anemia and malnutrition became the chief requisites for admission.

It is questionable whether the children of an open air school, with the requirements for admission such as were fixed in the St. Louis school, can be compared to the group of children which would come either to a pediatric dispensary or would apply for admission to a children's hospital. I lay stress upon the possible differences existing between the group concerning which I wish to report and other groups

upon which series of Wassermann reactions have been carried out, in order to possibly explain the wide differences existing between the results I have obtained and the results obtained by others working with large groups of children in hospitals or dispensaries. The great majority of these children with whom I have dealt in this group would probably not have sought medical advice.

In this work I have used cholesterinized and noncholesterinized alcoholic extracts of healthy human heart muscle or plain alcoholic extract of guinea pig heart, but have relied mainly upon the cholesterinized extracts in making reports, largely for two reasons: first, because I believe that the cholesterinized extracts are the more delicate and uniform; second, because the other reagents used in the test have been quantitatively standardized for the use of the cholesterinized antigens. The plain alcoholic extracts have checked, I believe without exception, in the four plus cases, and have shown positive results in the three plus cases, but are almost uniformly negative in the two plus and one plus cases. I do not in any way attempt a comparison between the relative values of the cholesterinized and noncholesterinized antigens, because, as I have said, I had tried to standardize my test for use with the cholesterinized antigens, and if a comparison of antigens were my object, I should have run the alcoholic extracts separately and adjusted the other reagents and conditions to suit the requirements of plain alcoholic extracts.

One of the chief points of interest in this work is the fact that these children were repeatedly examined by several different physicians. They are examined carefully and thoroughly at regular intervals by the physicians of the open air schools. They have been examined by various physicians in the dispensary of the St. Louis University, and also in other clinics. In only a few cases were any definite diagnoses made except of anemia and malnutrition, and in those few cases there was a difference of opinion among the clinicians who made the examinations.

A moment's reflection upon the source of the material in this series will bring to mind a number of the difficulties which were met in pursuing this work, and which tended to interfere with the best possible management of the material. There was a constantly changing enrollment in these schools; parents failed to assist examination and treatment, in many cases through indifference; often even active opposition developed. As soon as the blood findings were reported a

number of cases were taken in charge by private physicians and it became impossible to further follow these cases. A few mothers came to the clinic to protest against treatment, and in almost all such instances we fortunately succeeded in obtaining the mother's blood for examination. Although we endeavored to get the parents' blood for examination in as many cases as possible, we were successful only in those cases who came to protest against the work. The home environment in most cases seemed to be of the very worst. The visiting nurse reported that some of the fathers were living with two or three women, or, in other instances, that the mothers were constantly under the influence of alcohol, points which must be taken into consideration in drawing conclusions. Furthermore, although the authorities, as individuals, aided the work in every way possible, the fact remains that our relationship to the cases was entirely unofficial, and we had no authority whatsoever over either children or parents.

#### REVIEW OF CASES

Practically without exception the diagnosis in these cases was anemia and malnutrition. There were a number with spinal curvatures, contracted tendons, etc. In 1915 there were a few cases admitted who had slight heart lesions, but in 1916 all such cases are rigidly excluded. There was a definite diagnosis from clinical evidence in nine cases; five lues; three orthopedic cases; and one chronic bronchitis. In all, 224 children were examined for the reaction of their sera with syphilitic antigens, with the following results.

37 cases, or 16.5%,	reported four plus
39 " " 17.4%,	" three plus
22 " " 9.8%,	" two plus
28 " " 12.5%,	" one plus
98 " " 43.8%,	" negative

If the one plus cases are counted as negative, there are 43.3 per cent positive. Of the whole series 33 per cent shows three and four plus Wassermanns. In all, 56.2 per cent of the cases shows fixation of complement.

The Wassermann test was done on two days of each week, and the number of serums examined from other sources was practically the same as the number from the open air schools. Of the cases from other sources I reported 10.9 per cent positives as compared with 56 per cent from the open air schools.

For the von Pirquet I used undiluted "O. T. human type," and as a control, the glycerinized bouillon evaporated to one-tenth its bulk. In 221 cases the von Pirquet was positive in 93, or 42 per cent. Von Pirquet was negative in 110 cases, or 50 per cent; and doubtful in 18, or 8 per cent.

The ages of the children ranged from six years to twenty years. There were four cases six years old, three were fifteen years old, one nineteen years old, and one twenty years old. One hundred and fifty-five were between the ages of eight and thirteen years, and of this number 59 per cent gave positive von Pirquets.

## COMPARATIVE FIGURES BY AGE

Age	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Negative	2	5	7	11	16	11	17	12	5	2	0	0	0	1	0
Positive	2	2	4	20	16	15	16	21	9	1	1	0	0	0	1

## COMPARISON OF SYPHILITIC AND TUBERCULOSIS REACTIONS

Cases showing both positive Wassermann and positive von Pirquet	20.7%
Cases showing both negative Wassermann and negative von Pirquet	14.0%
Cases showing positive Wassermann and negative von Pirquet	27.0%
Cases showing negative Wassermann and positive von Pirquet	20.0%

On the basis of the clinical findings there were three cases diagnosed as congenital lues. In the three cases the Wassermann was clearly negative, and repeatedly so. Two other cases in which the clinical evidence was strongly presumptive of congenital lues, gave one plus Wassermann reactions. These findings are in distinct contrast to those of Veeder, who found that all cases which were clinically frankly syphilitic gave also positive Wassermans. In those cases showing positive von Pirquets the clinical evidence, although not positive, was in general quite strongly presumptive of tuberculosis. There were some three or four cases in which positive diagnosis was made and tubercle bacilli found in the sputum.

## COMPARISON OF CLINICAL AND SEROLOGICAL EVIDENCE

I think the men who have examined these cases will agree with the statement that in general those children showing a positive von Pirquet, showed clinical evidence of tuberculous infection. With the Wassermann positive cases, quite the reverse was true. In those cases in which one of the clinicians was most confident in his

diagnosis of congenital lues the Wassermanns were negative, and were repeatedly negative. In a few cases in which the clinical evidence seemed strongly presumptive of lues, the Wassermann was reported as one plus, or two plus. In the vast majority of those showing four plus Wassermanns the clinical evidence was practically negative. In fact, the four plus Wassermann cases were among the best physical specimens in the schools. I will cite a few cases to illustrate:

S. B. Age 9. Father and mother living and well. Two brothers died of tuberculosis. Patient is fairly well nourished and apparently well. Physical examination, negative. Wassermann four plus. Gluteal injections of mercury salicylate begun May 3, 1916, and continued each week to July 3, 1916. On November 3, 1916, the Wassermann was still four plus.

I. P. Age 11. Family history negative. Patient complains of headaches and nervousness. Physical examination: Mitral bruit with heaving impact and a marked second aortic sound. Cardiac left slight hypertrophy. Knee jerks normal. Pupils quite sluggish. Wassermann three plus.

V. P. Sister of last patient. History negative. No particular reason for going to open air school. Physical examination: Mitral bruit with heaving impact, and a marked second aortic sound. Knee jerk three plus. Pupils quite sluggish. Hutchinson's teeth. Looks quite anemic. Wassermann two plus.

The first case is negative clinically but gives a four plus Wassermann. The second case has symptoms scarcely more than suggestive of lues, with a three plus Wassermann. The third case, a sister of the second case, has strongly presumptive clinical evidence with a two plus Wassermann. These cases were selected to illustrate what seemed to be the relation between the Wassermann findings and clinical evidence in a considerable proportion of this series.

I may carry the illustration further by citing another case:

R. B. Age 13. Father and mother living. No brothers or sisters. Patient retarded physically and mentally. Very nervous. Physical examination: Prominent bosses, arched palate. Pupils, no excursion. Left knee jerk greater than right. Diagnosis: congenital lues. The Wassermann was clearly negative. Ten gluteal injections of mercury salicylate were given, and the Wassermann repeated with negative result. After another series of ten injections, and a rest for six weeks, the Wassermann was again repeated and reported clearly negative. Treatment had no noticeable effect on this case either serologically or clinically.

Another interesting case is that of a boy 12 years old. In February, 1916, his physical condition was rather above the average of the children in the

school. Physical examination was negative, except for anemia and malnutrition. There was a history of syphilis in the family, and the patient had been treated at an earlier date for a syphilitic skin lesion. The Wassermann was four plus. Von Pirquet strongly positive. He was given ten injections of mercury at weekly intervals, without any apparent result. He then left the school. In September, 1916, he came to the eye clinic and was treated for luetic keratitis. He was later treated in the City Hospital for severe lesions of both eyes, and syphilitic arthritis of both knees.

The specificity of the Wassermann reaction is still being discussed, and a great deal is being published with reference to the interpretation of the weaker reactions with cholesterinized antigens. From these cases it seems perfectly clear that the reaction under any circumstances can be interpreted only as a single symptom, and must have corroborative evidence to be conclusive. There are certainly weak reactions which are non-specific, but in other cases with the same technic one will get weakly positive reactions in unquestioned cases of lues, as shown by the cases cited below.

F. P. Age 14. Family history negative. Patient is well developed and well nourished, and his history is negative except for a chorea two years ago. Physical examination negative. Wassermann one plus.

I. W. Age 13. Family history negative. Patient well nourished and well developed. Apparently well. Physical examination; sluggish pupils, palpable radials, exaggerated but equal reflexes. Urine examination shows abundant albumin, and a moderate number of granular and hyaline casts. Wassermann one plus. Assuming a diagnosis of luetic nephritis, deep injections of mercury were begun. The albumin and casts disappeared from the urine in a few weeks. After two months of treatment the patient left the school, but reported for several weeks for examination. The urine remained free from any trace of albumin. The mother's blood was secured for examination and was reported four plus. The mother also gave a history of rheumatism.

Another interesting case with a one plus Wassermann gives the following history:

L. T. Age 9. Father paralyzed in one leg. Mother has tuberculosis. One brother at sanatorium for tuberculosis. Two sisters are well. Patient is very nervous. Physical examination shows enlarged postcervical and epitrochlear glands. Pupil reaction normal. Knee jerk absent. The patient was put on injections and one month later the mother came to the clinic to see that the treatment was stopped. The mother stated that the father had suffered a stroke of paralysis affecting one side of his body some four years ago. The paralysis came on slowly, requiring about two weeks to involve all of one side. He recovered in about five weeks in one of the hospitals of the city,

where he was treated by mercury rubs. Under considerable protest I got the mother's blood for examination, and found a four plus reaction.

## TREATMENT AND RESULTS

When possible, each case whose Wassermann was reported positive was placed under treatment. Injections of mercury salicylate into the gluteal muscle was chosen as the most practical method. The treatment was begun in about seventy-five cases, and of that number about fifty remained under treatment and observation for three months or longer. I have repeated the Wassermann on thirty-six cases that have been on treatment for ten weeks, and off of treatment for three months. Nine of the thirty-six cases remained unchanged. Of these, three cases which were four plus remained four plus; three cases which were one plus, remained one plus, and in no case did a one plus become negative. The number is too

GAIN IN 5 MONTHS OF 25 CASES GIVING							
POSITIVE WASSERMANN'S AND NEGATIVE VON PIRQUETS				NEGATIVE WASSERMANN'S AND POSITIVE VON PIRQUETS			
CASE	MONTHS IN OPEN AIR SCHOOL	GAIN IN WEIGHT		CASE	MONTHS IN OPEN AIR SCHOOL	GAIN IN WEIGHT	
1	17	10	lbs.	1	5	6	lbs.
2	14	11	"	2	13	16	"
3	9	0	"	3	18	11	"
4	17	4	"	4	17	8	"
5	11	13	"	5	6	3	"
6	11	3	"	6	17	27	"
7	17	4	"	7	5	4	"
8	7	1½	"	8	17	18	"
9	17	7	"	9	6	3	"
10	17	12	"	10	6	8	"
11	14	11	"	11	17	10	"
12	8	9	"	12	16	8	"
13	14	6	"	13	9	6	"
14	12	4	"	14	6	2	"
15	8	10	"	15	16	18	"
16	23	6	"	16	16	20	"
17	15	13	"	17	16	13	"
18	14	0	"	18	16	26	"
19	16	9	"	19	17	16	"
20	16	5½	"	20	17	12	"
21	17	9	"	21	7	5	"
22	14	6	"	22	8	19	"
23	13	3	"	23	7	15	"
24	14	6	"				



small for definite conclusions, but the greatest change in the serum reactions was in cases which gave three and four plus reactions before treatment.

There were twenty-five cases with a negative Wassermann and positive von Pirquet, who remained at the open air school for five months or longer, a list is given showing the number of months in residence and the gain in weight. A comparison of the cases in this group with a similar number who gave positive Wassermann and negative von Pirquet, shows that those in the first group made a decidedly greater gain in weight than those in the last group. The difference in the mental ability, and nervous constitution in these two groups makes quite a contrast. Of those showing positive Wassermann reactions practically all were definitely neurotic. Extreme nervousness, fainting, crying without any cause, and vomiting from riding on the street car was very common.

While these figures are suggestive, they can not be accepted as the basis of an exact comparison. The greater gain in weight shown by the von Pirquet positive group may depend upon many factors, certainly the ages of the children in the two groups would influence the results. It is at present impossible owing to the discontinuance of this work to obtain the exact data—again our lack of complete control of the material interfered with the work.

#### DISCUSSION AND CONCLUSION

It is apparent that certain of the results obtained by the serological examination of this group of children are rather startling. The more, since they are startling, must one hesitate to draw definite conclusions. It is probable that these results should be considered only as suggestive. It is certain that I have no desire to draw sweeping conclusions.

In the first place, examining a large group of children drawn from the public school population of the City of St. Louis, and grouped chiefly because they show, in common, evidence of anemia and malnutrition, we find somewhat over 33 per cent show a positive Wassermann (either a three or four plus). We are certainly justified in considering these children as congenital syphilitics, especially when there are even slight clinical evidences of lues.

We find further that approximately an additional 23 per cent of these children showed a one or two plus Wassermann. It has

never been accepted that a weak Wassermann reaction signifies the absence of syphilis; I do not mean on the other hand, to state that a one or two plus reaction signifies infection; but it is unquestionably true that certain of the children showing the weak reactions did show fairly definite clinical evidence of lues, certain ones of this group also showed symptoms at least suggestive of syphilis and certain ones of this group have either sisters or brothers or possibly parents giving positive Wassermanns (that is, three or four plus). It is probably not too bold to conclude that some of the children in this group of approximately one quarter of the children examined were syphilitic.

. We are, therefore, forced to accept the fact that between 33 and 56 per cent of the children in this group were syphilitics and there is very little doubt that they are congenital syphilitics.

Possibly the greatest difficulty met in interpreting these results is the matter of what is to be considered as clinical evidence of syphilitic infection in children. Are certain conditions, such as neurotic symptoms, abnormalities of ocular or tendon reflexes, or local or even general adenopathy, to be considered as evidence of congenital lues in the absence of a positive Wassermann (either negative or one or two plus)? Our lack of cut and dried rules for diagnosis makes the definite interpretation of certain of the results impossible; while my personal opinion is that a large percentage of these children who showed a one or two plus Wassermann and who also showed certain of the clinical evidences suggestive of syphilis, were actually syphilitics, I do not wish or intend to be dogmatic in statement.

While I do not consider it advisable to place great stress or reliance upon slight evidence of results of treatment, it is possibly worth while to note the fact that the instructors in this open air school, reported the children which were given antiluetic treatment, showed improvement in mentality and deportment—this applied to practically all children so treated, whether giving strong or weak syphilitic fixation reactions. How much of this improvement was due to the life in the open air, the better care given the children during the school hours, and possibly better nourishment can not, however, be determined definitely.

Since I have handled this material and these results chiefly from the viewpoint of the serologist, and since I am unable to obtain a

definite diagnosis in many of these cases of suspected syphilitics giving a one or two plus Wassermann, and on the other hand, since the clinicians who have handled these children are unwilling to flatly deny the existence of luetic infection in many of these cases, I hesitate to make any sweeping assertion regarding the value of the Wassermann in congenital syphilis without frank manifestation.

I do, however, believe that my results suggest that considerable caution must be exercised as regards the interpretation of a negative or weak Wassermann reaction in a child suspected of congenital syphilis.

## THE VALUE OF THE COMPLETE EXAMINATION OF THE EAR IN SYPHILIS\*

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THE preponderance of evidence drawn from many investigations goes to show that the eighth nerve is more often attacked in all stages of syphilis than any other of the cranial nerves and that the lesion is a true neuritis of its nuclei, its trunk, or its peripheral distributions. The significance attached to the diagnosis of a syphilitic auditory neuritis is of far greater magnitude than simply the determination of the etiologic factor responsible for the aural disease, and such a lesion may not be treated as a clinical entity without considering it indicative of a luetic invasion of the central nervous system. Cerebrospinal syphilis is by no means always a late manifestation of the infection, and the classic objective signs, such as the Argyll Robertson pupils and the diminished or absent tendon reflexes are, in fact, late symptoms that indicate an actual involvement of the brain or cord substance.

Aural symptoms may arise during the vascular or the meningeal stage of the brain invasion. Tinnitus, deafness and vertigo, in the order named, are the symptoms of an auditory neuritis, but it must be remembered that the onset may be very insidious, and for this reason it is important that certain characteristics be recognized as early as possible. The internal ear and the eighth nerve have two separate and distinct functions, audition and equilibration. From the internal ear to the central origin of the eighth nerve these functions are anatomically and physiologically distinct, and by the newer and more accurate methods of otologic examination it is possible to separately test both the cochlea and the vestibular functions; there-

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\*The otologic side of the investigation was presented before the American Otological Society, Atlantic City, May 31, 1917, under the title, "The Static Labyrinth in Syphilis." This paper contains only those points which may be of interest to the syphilographer.

fore, localization of eighth nerve lesions has passed beyond the stage of hypothesis. The deafness due to a syphilitic acoustic neuritis may be very slight and the patient may hear the voice surprisingly well; such cases, however, present the form of deafness which is most characteristic of lues and which, indeed, is considered by some authorities as pathognomonic. The typical hearing defect, as physically impossible as it may seem, is a shortening of the duration of perception for a tuning fork by bone conduction out of all proportion to the shortening of the duration of the perception for the same fork when it is heard by air conduction. Good hearing is preserved for the forks of low pitch when heard by air conduction, but the high sounds are badly heard. Vertigo, nausea, vomiting and a spontaneous nystagmus are the principle symptoms indicating involvement of the static labyrinth. In syphilis the three last mentioned symptoms are not common, and a history of vertigo may have to be elicited; this may be the case when the static labyrinth is found on examination to be completely "dead."

The tests of the static apparatus, for the devising of which Robert Bárány, of Vienna, received the Nobel Prize in Medicine, give very constant results in normal individuals. The tests are based on the over-stimulation of the terminal nerve fibers in the ampullæ of the semicircular canals and in the vestibule. This stimulation is produced by a movement of the endolymph set into action by rotating the individual in a smoothly revolving chair of special design, or by douching the ears with water above or below the temperature of the body. The objective evidence of the stimulation is a nystagmus depending in character upon the set of canals which are stimulated; pastpointing of the extremities, depending upon the vertigo produced; and falling of the body to one side or the other.

Isaac H. Jones, of Philadelphia, has formulated a standard which has been accepted by the United States Government in the examination of applicants for the Aviation Corps. (See, Transactions of the American Otological Society for 1917.) After turning a person ten times in twenty seconds nystagmus should last for twenty-six seconds, a latitude of eight seconds is allowable. Vertigo should last for twenty-four seconds. On right turning both arms should pastpoint to the right and falling should be to the right. On left turning the opposite should occur. Douching the ear with water at 68°F. or at 112° F. will produce nystagmus, vertigo, pastpointing,

and falling in various directions depending upon the direction of the flow of the endolymph in the canals being tested.

The tests, of course, present details too numerous to be mentioned in a paper of this kind except to say that Jones,<sup>1</sup> and his co-workers, have succeeded in locating, and in postulating, with a high degree of accuracy the neuraxial tracts of the vestibular branch of the eighth nerve. They teach that each semicircular canal has a nystagmic tract and a vertiginous tract, and the tests, therefore, are particularly valuable in the localization of cerebellar and brain stem lesions. At least, we are able to say with a marked degree of certainty whether an eighth nerve involvement is intralabyrinthine, in the nerve trunk or central, and this is of great value in syphilitic auditory neuritis, as a brief review of the studies concerning the morbid anatomy of these cases will show that the nerve may be involved at any point in its course. Moos<sup>2</sup> in 1887 found changes in the vestibule, in the organ of Corti and in the ampullæ of the semicircular canals, but a normal nerve trunk, in a patient with secondary syphilis who died after ear symptoms had arisen. In tertiary syphilis Rosenstein<sup>3</sup> found lesions in the nerve stem, in the nuclei, in the roots, and, in one case, in the roots alone. Manasse<sup>4</sup> has given a most complete picture of the morbid anatomy found in a patient with tertiary syphilis who had been deaf for one year before death. He found changes in the nervous structures of the cochlea, in the semicircular canals, and also in the nerve trunk. In tabes with deafness Habermann<sup>5</sup> found gray atrophy of both auditory nerves and atrophy of the nerve endings in the cochlea and in the semicircular canals. The nuclei were intact, the lateral and median acoustic roots much atrophied. Bruehl<sup>6</sup> found degenerations in the nuclear region of the eighth nerve. Mayer<sup>7</sup> studied five cases of general paresis with deafness and found atrophy in all the nervous elements from the organ of Corti to the medulla. In 1912, Kniek and Zaloziecki<sup>8</sup> examined the spinal fluid in nine cases of nerve deafness in early syphilis and found a high cell count in all and a positive Wassermann in eight. They claim that deafness in early syphilis is due to a basal meningitis which involves the eighth nerve. Ellis and Swift<sup>9</sup> after a similar study concluded, "that all lesions of the eighth nerve are possible manifestations of a disastrous form of general infection—syphilis of the central nervous system." In substance, the authors urge the examination of the spinal fluid in all ear cases.

Willcut<sup>10</sup> believes that an involvement of the eighth nerve in early syphilis is due to a toxic irritation of the nerve sheath and the peripheral nerve endings.

A clinical study of patients with syphilitic deafness by the Bárány methods, in my experience, has indicated lesions in all portions of the aural nervous apparatus. In the last eighteen months I have had the opportunity of making an ear examination of a creditable number of patients with syphilis and syphilitic central nervous system lesions. Many of these patients have been examined, with the cooperation of Dr. A. C. Gillis, in the Neurologic Clinic of the Mercy Hospital; some of them did not complain of ear symptoms though it was not difficult to demonstrate the associated aural implication. A number presented predominant ear disturbances, and in a few instances the examination of the ear led to the diagnosis of cerebrospinal disease. Though the hearing was abnormal in the majority of the cases, the tests of the static labyrinth, by rotation and cold douching, were of far greater value in confirming the presence of a lesion in the nervous apparatus of the ear than were the tests of audition. Generally speaking the abnormal responses of the static labyrinth in syphilis may indicate a lesion of the vestibular nerve at any point from its nuclei to its peripheral distributions. If we may have "islands of deafness," we may likewise have *islands of static inhibition*; and should these vestibular defects be situated neuraxially, the reactions from the vestibular tests may simulate those seen in brain-stem or cerebellar tumors. In syphilis the neuraxial signs are likely to be so atypical that they indicate lesions of such widely separated areas that simultaneous involvement of these tracts by a new growth would be impossible, whereas a luetic degeneration of these pathways is possible and not improbable. The most characteristic reaction of syphilitic vestibular disease is a lowering and a confusion of all the responses from the static labyrinth, this may vary from the totally dead labyrinth giving no response to the cases showing normal responses reduced in degree. Increased irritability of the static labyrinth, evidenced by prolonged nystagmus with nausea and vomiting is a sign which may not be overlooked. Crossed pastpointing may be present. Variations from time to time in all the responses must be expected and may be of value in following the progress or retrogression of the disease. The vestibular tests, in most instances point to the ear

which is most involved and in syphilis both ears are usually affected.

I have chosen for study twenty-eight case histories of patients in whom the diagnosis of syphilis has been positively established not only by clinical evidence but by laboratory methods; the number is far too small to be of statistic value, but the data obtained has been of marked clinical advantage. The cases are arranged in two series; first, those patients in whom the ear symptoms were of a predominant character, and second, those patients with central nervous system lesions upon whom an ear examination was made irrespective of aural complaints. There are twelve patients in the first group who came complaining of deafness, and tinnitus. Vertigo was not voluntarily mentioned, though a history of it was obtained in five patients. Although the cochlea is usually considered to be the oftener attacked, the complete otologic examination in these cases showed both the cochlea and the vestibular function to be involved. Five of these patients were the victims of hereditary syphilis, four of whom had had interstitial keratitis. This group of cases showed all the variations of abnormal vestibular response. The blood Wassermann was positive in all twelve cases. In only one instance was the hearing totally destroyed and in this child the static apparatus was also completely functionless. Most of the patients could hear the voice without much effort and the Bárány tests were of more service in correctly locating the lesion than were the tests of audition. In several cases, where a history of lues could not be obtained, the distinctive ear symptoms were confirmed by the laboratory findings:

#### CASE I

K. H., age 18, admitted August 1, 1916, complaining of slight deafness which had started July 1st with tinnitus. The hearing tests were uncertain but there was a definite shortening of bone conduction, which in a person of her age is always to be regarded as pathologic. The vestibular tests were confusing, conflicting and abnormal. Her blood Wassermann was positive and her ear condition improved under vigorous treatment.

In several instances patients who came to the ear clinic were later referred to the neurologic clinic because the ear symptoms of which they complained were of but secondary importance. One case is worthy of record.

#### CASE II

E. R., age 38, colored, admitted July, 1916, complaining of tinnitus and deafness. The hearing defect was typically luetic and the vestibular apparatus



showed great irritability, nystagmus lasting from fifty to sixty seconds and being accompanied by nausea and vomiting. The blood Wassermann was negative and a provocative Wassermann was negative. At this time there were no neurologic signs. The woman was urged to have a spinal puncture but refused, and drifted away from the clinic. In May, 1917, she returned feeling much worse and showing a marked degree of deafness. Her pupils were small, unequal, and sluggish to light. She consented to a spinal puncture, which showed: Cell count, 31; Wassermann strongly positive; globulin tests positive. (Spinal fluid examination by Dr. Moore.)

In the second group there are sixteen cases which may be classified under the headings of the diagnosis of cerebral syphilis, tabes dorsalis, and general paresis. Seven of these patients may be classified as early brain cases. They came with the complaint of severe vertigo and the static labyrinth was found involved in all the vertiginous cases. The Romberg was positive, or suggestive, in all, which is confirmatory of the aural nature of this sign. Several cases are of sufficient interest to be briefly reported.

#### CASE III

W. G. M., age 25, male, white, admitted July 27, 1916, complaining of severe vertigo. Romberg positive. Neurologic symptoms suggested a cerebellar tumor. Hearing normal. Vestibular tests indicated neuraxial lesion of wide extent. The responses were confusing and variable from day to day. The patient denied lues and the blood Wassermann and the provocative Wassermann were negative. The spinal fluid showed: Cell count, 42; Wassermann inconclusive; globulin tests strongly positive. On August 30 the patient became suddenly and completely deaf in the right ear. He died September 15, 1916, and a postmortem showed an old syphilitic basal meningitis and a degenerated gumma in the middle lobe of the cerebellum extending to both lateral lobes.

#### CASE IV

Chas. L., age 47, white, admitted August, 1916, complaining of sudden and complete deafness and severe vertigo of ten days' duration. Romberg positive. Static labyrinths practically without response. Blood Wassermann positive. Spinal fluid: Cell count, 20; Wassermann strongly positive; globulin tests strongly positive. This man died a few weeks later but a postmortem could not be obtained.

Seven cases of tabes dorsalis have been included in this group, four of whom had primary optic atrophy. In four of this number the cochlea and vestibular branches of the eighth nerve were both involved, in one the cochlea function alone was involved, and in two the hearing was apparently normal though the static function

was abnormal. As would be expected these tabetic cases showed clear cut defects. In one case of the cerebellar type of tabes, it was possible to surmise just the point in the brain stem which was the site of the lesion. One case of general paresis showed complete reversal of all the pastpointing responses. Finally I wish to report one case which is open to question. (Special fluid examinations in Cases III and IV by Dr. Judd.)

#### CASE V

I. H., age 43, white, male, was referred by Dr. Harry Friedenwald. The man had a history of two severe attacks of vertigo. Examination showed a moist perforation of one drum membrane from an old suppurative condition. The hearing, of course, was defective but there was an element of perceptive deafness as well as of conduction. The vestibular tests showed a lowering and a confusion of the responses. The man admitted syphilis, the primary lesion having occurred five years before, but he had had no treatment for some years. His blood Wassermann was negative. His spinal fluid showed: Cell count, 12; Wassermann negative; globulin faintly positive. Under treatment there have been no further attacks of vertigo. In this case have we made an extremely early diagnosis of syphilitic meningitis? (Spinal fluid examination by Dr. Baetjer.)

It is hardly necessary to say that the pathology of these auditory cases is probably first a toxic irritation from an infected spinal fluid which is followed by an involvement of the nerve tissue itself. The eighth nerve is devoid of neurilemma and its location would make it the most liable to attack. Ellis and Swift<sup>9</sup> have shown that the prognosis need not be so grave concerning deafness if the diagnosis is made during this stage of irritation, but they have also warned that there is a graver issue at stake. It is hardly within the province of the otologist to meet all the problems of brain syphilis, but to be a successful clinician in any line, "one must know syphilis."

Hutchison and Jackson,<sup>11</sup> in 1861, showed the frequency and correctly defined the nature of deafness in hereditary syphilis. Habermann,<sup>5</sup> in 1896, reported sixty-six cases of syphilis of the internal ear, thirty-four of which were in the secondaries. Mayer,<sup>7</sup> in 1911, reported sixty-five cases, thirty within the first year of the infection, and thirteen within from three to ten weeks after the primary sore. Politzer<sup>12</sup> reported one case occurring seven days after the chancre. None of these cases had had salvarsan to the use of which so many lesions of the internal ear have been accredited in recent years. In 1915, G. W. Willcut<sup>10</sup> reported the results of an examination of 293

syphilitics seen in Urbantschitch's Clinic. None of the cases had had salvarsan, indeed the Wassermann reaction was still negative in many, yet in fifty-six cases of a month's duration or less, he found fifty-two with a characteristic auditory lesion. Deafness in tabes has been called attention to by Glogau,<sup>13</sup> Ellis and Swift,<sup>9</sup> Shaller<sup>14</sup> and many others.

Although the bibliography of syphilis of the ear is most extensive, there is one point which it seems is somewhat misunderstood in spite of all that has been written, and that is that the deafness, or any of the ear symptoms due to syphilis, need not be profound; the marked cases are, in fact, the exception rather than the rule. The ear lesion, in its incipiency, is, however, none the less indicative of the disease that is its cause, and the signs may be all the more characteristic. The otologist may not disregard the significance of syphilitic acoustic neuritis as an early indication of an invasion of the central nervous system; and a complete examination of the cochlea and vestibular apparatus, made with due precision, can be of value to the syphilographer and the neurologist.

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# THE PRESENTING SYMPTOMS IN THREE HUNDRED CONSECUTIVE CASES OF SYPHILIS\*

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WHETHER a man be a surgeon, ophthalmologist, dermatologist, internist, neurologist, gastroenterologist, or general practitioner, the subject of syphilis is of paramount interest and importance. Of all the diseases to which man is heir, it takes the most diverse and varied forms and it is by no means uncommon. It has been estimated that between 10 and 20 per cent of the adult male population has the disease. It is claimed that there are 200,000 syphilitics in New York City alone. It causes 42 per cent of all miscarriages, and 75 per cent of the children of syphilitic parents die in infancy. Those that survive in many cases would be better dead.

We hope, in presenting this paper, to show to some extent the great variety of ways in which it manifests itself, and thus to influence the profession to take cognizance of this great plague and to remember that it may have an important bearing on many an obscure case. There was some excuse for the older practitioners not recognizing the disease, since, in many cases, especially in women, its beginning may be obscure. The primary lesion may not be noticed and the secondary may be either slight or thought to be some other malady. Today we can hide behind no such excuse with the Wassermann reaction at our very hand. We do not pretend to say that this test is absolutely accurate and infallible. Nothing man made is perfect. But in a vast majority of cases it gives us the information we need. We find many modifications of the original technic, but believe that the original test is still recognized as the best, with Noguchi's modification giving it a close second. We have tried out the Hecht-Weinberger modification, and do not find that it has any advantages over a carefully done Wassermann.

The bichloride test, as recently devised, has not been accepted as serviceable, and if done at all is used by only a very few.

The luetin test we have used to a considerable extent and find

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that it is of value in certain tertiary forms in which the Wassermann is negative. The gold chloride test combined with a careful examination of the spinal fluid is of inestimable value in spinal and cerebral lues.

The microscopical examination for the spirocheta pallida either by the dark-field or by the staining method is of the greatest value although it is true that in very many of the cases with a primary lesion it is almost impossible to demonstrate the organism since the patient has often treated the sore for several weeks and in many cases it has been cauterized several times either by the doctor or some knowing friend. It is undoubtedly safest "to consider every venereal sore as potentially a chancre," even if it does not present the distinguishing characteristics and to withhold a definite diagnosis until it has been proved negative by watchful waiting and several Wassermann tests.

In this series we have chosen our last three hundred cases, since our records before these are not as complete as we would wish to have them.

## CLASSIFICATION OF PATIENTS ACCORDING TO PRESENTING SYMPTOMS

PRIMARY	55	EAR		2
SECONDARY	42	Deafness	1	
ULCERS	54	Roaring	1	
Throat	26	NERVOUS		33
Leg	19	General	16	
Breast	2	Paresis	8	
Arm	1	Tabes	4	
Cervix Uteri	1	Cerebral	3	
Neck	1	Facial	2	
Nose	1	GUMMA		16
Toe	1	Testicle	7	
Finger	1	Penis	4	
Clavicle	1	Bladder	1	
CONDYLOMATA	3	Kidney	1	
Rectum	2	Humerus	1	
Vagina	1	Jaw	1	
MUCOUS PATCH	26	Epididymis	1	
Mouth, Nose, Throat		MISCELLANEOUS		13
GENERAL GLANDULAR	16	Nephritis	3	
GASTRO INTESTINAL	11	Diabetes	2	
PAIN	22	Liver	2	
Head	10	Heart	2	
Side and Shoulder	7	Anal Fistula	1	
Abdomen	1	Pernicious		
Arm	1	Anemia	1	
Leg	2	Swollen Face	1	
Hip	1	Dizziness	1	
EYE	7	Total		300

The Wassermann reaction has been done on all the cases, and the other tests in many of them and, omitting the primary form, practically all have shown a positive blood or spinal fluid. In a large number of the primary lesions the organism was found. In cases diagnosed clinically with negative Wassermann and when no organism was discovered, the diagnosis was confirmed by the therapeutic test.

The preceding chart shows in tabulated form the presenting symptoms for which the patient asked relief. In not a few cases there were several prominent symptoms, but we have classified the patient under the one of which he complained.

Of the fifty-five cases with a primary lesion, all except three were on the genitals. There were two on the lip and one, in the case of a doctor, on the finger. It is surprising that we should not have a much larger number showing a primary lesion, but since quite a large number of them were referred, and because few physicians are fitted to do the dark-field examination, we would expect many of them not to be referred until some further symptoms than the primary sore was evident and this likewise accounts for the rather large number of secondary cases that we have in this series. Under the division marked secondary we have placed only those showing the rash, and those with mucous patches, condylomata, etc., under separate headings.

Under the head of ulcer there were fifty-four cases. It is difficult to draw a sharp line of division between mucous patches and ulcers. However, we are calling ulcers those lesions in which the necrosis seemed to involve a deeper layer than the mucous membrane. It is rather striking that twenty-six or practically half of these ulcers were located in the throat and that nineteen were found on the leg. The remaining six were sufficiently well distributed to show that no portion of the body is exempt.

There were other cases than these three mentioned that had condylomata, but these were the only three that came in complaining of this symptom as the chief trouble.

Although the mucous patch is a very constant and characteristic lesion of late secondary syphilis, of the seventy-one cases in this series that were secondary, only twenty-five came in complaining of the mucous patch and all of these were in the mouth, nose or throat.

By placing a special heading "General Glandular Enlargement"

we do not mean that these sixteen were the only cases that showed this condition, but these were the ones that came in complaining solely of this. Some of them had only very slight enlargement of the lymph nodes while in others the enlargement was very marked. It is true that glandular enlargement is found to some extent in practically all cases of lues.

We do not pretend to say with reference to the next two divisions; viz., gastrointestinal symptoms and pain, as well as certain other conditions, that lues was the only cause, but when the Wassermann was positive and when the symptoms were relieved by salvarsan and mercury we feel justified in attributing the trouble to syphilis. The eleven gastrointestinal cases presented very diverse symptoms, varying from acute gastritis and colitis to what the patient would call "indigestion" or "stomach trouble."

The twenty-two cases of pain were fairly well distributed over the body and we were able to find no other cause for it than lues, and as specific treatment cleared it up in every case we felt justified in giving lues as the etiology. It is hard to say exactly to what direct cause the pain in these cases is due. It is very striking that practically half of them are located in the head. Some would undoubtedly come under the classification of toxic, others hypertension, and in a few cases the pain was so intense that one naturally thought of cerebral gumma. This symptom of headache being present in  $3\frac{1}{3}$  per cent of the cases suggests that lues might play an important part in the etiology of our chronic headaches.

Seven or a little over 2 per cent came in with eye symptoms. Iritis and interstitial keratitis are the chief troubles for which those patients were referred. Two cases of keratitis were congenital.

Of the thirty-four nervous cases, sixteen are classed as general nervousness. This is, of course, a vague sort of symptom and undoubtedly was in a few instances syphilophobia, others would say "so nervous can't work" or "can't sleep" or some such expression and this would be the only symptom that could be elicited. Two cases came with facial paralysis, three with marked cerebral symptoms, four with tabes, and eight with paresis.

Our series shows only sixteen with gumma. If many of the other cases could have been investigated more fully or had come to autopsy, more gummata would undoubtedly have been found. Probably some

of the gastric symptoms were due to gumma and it is very likely that at least one of the liver cases would have shown gumma of this organ.

Under the heading of miscellaneous we find a few interesting cases. Of the three cases of nephritis there is a bare possibility that one of them had the trouble brought on by excessive mercury therapy before coming to us, and in the other two cases the trouble seemed to be purely of luetic origin. We have found but one other case of pernicious anemia in literature that had lues given as the cause.

Finally we would like to emphasize what is already well known, viz., the great majority of the presenting symptoms and to call attention to the fact that even in this series some of the very important and often recurring types are absent—for example, the vascular cases. We think these are absent because the subjective symptoms are either vague in themselves, or they are referred to other organs—as headaches, dizziness, etc. In two or three cases aneurysm was found. In a good many arteriosclerosis was present, but this was found only upon examination and, of course, was not mentioned by the patient.



## THE PROVOCATIVE WASSERMANN TEST IN THE CLINICAL DIAGNOSIS OF SYPHILIS

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**C**RITICAL revision of first conceptions has overtaken, one by one, our most cherished diagnostic tests, and placed qualifications upon their usefulness which make their correct interpretation and wide application increasingly difficult. Even so striking and valuable a generalization as that which forms the foundation of the Wassermann test has been subjected to so many readjustments with the advance of knowledge that the clinical syphilographer is at times almost disposed to underrate it. On the other hand, the general diagnostician, hard pressed for a means of rapid decision in a case, frequently overrates it. In particular the negative Wassermann reaction has had to bear the brunt of the assault on the test, and it is probably for this reason that any means of making a negative Wassermann test positive has met with especially enthusiastic acceptance.

The so-called provocative Wassermann test is based upon an observation made by Gennerich in 1910 and confirmed by Milian, to the effect that a syphilitic serum weakly positive or even negative before, can be rendered strongly positive following an injection of salvarsan. Gennerich conceived the reaction to be a phase of the Herxheimer reaction, and ascribed to it considerable value in the detection of latent syphilis, especially in cases in which treatment had been given followed by a rest period. Under the advocacy of Lier, Hoffmann, Lerredde, Fordyce and other syphilographers of large experience, and following the encouraging reports of Pease and Craig as to its usefulness, the procedure is gaining currency as a method of diagnosis, and as a prerequisite to a decision as to whether or not a patient is to be discharged as cured. A dissenting voice has, however, recently been raised by King, who, in a limited number of cases, could find little evidence of a provocative effect produced by an injection

of salvarsan in syphilitics. He pointed out, moreover, that the work of Boas, and a careful analysis by Haller of the factors of technical error and variations in the reagents used in the Wassermann test, might explain the apparent reversal of reactions under the influence of salvarsan. Haller believes that little variation occurs in the syphilitic serum itself. King proposes as an essential condition of a valid provocative procedure, that all the tests both on blood drawn just before and after injection should be performed at one sitting with the same reagents, thus reducing to a minimum the factor of technical variation. In estimating the significance of a provocative procedure, attention must also be drawn to the bearing of Craig's work upon Wassermann variations in untreated cases. In a long series of cases under carefully controlled conditions, he found in seemingly diametric opposition to Haller, that wide fluctuations could occur within a very short time (as short as one day) in the complement fixing power of the serum of a given syphilitic patient. Between the two views there is little recourse to argument, and the presumption is that both factors play a part in actual practice. Craig vigorously advocates the provocative as a diagnostic procedure and a means for controlling the effect of treatment.

It must be conceded that if the provocative procedure is to have any value for diagnostic purposes it must be cleared by painstaking investigation from the charge of being merely a product of technical or fortuitous variations in the behavior of the reagents or of obscure and independent changes in the patient's serum. The number of provocative reactions thus far reported seems scarcely sufficient to show a degree of uniformity in the production of provocative effects sufficient to completely eliminate the possibility that they occur independently of the injected therapeutic agent. Nor can the Wassermann test itself be regarded as yet as a procedure sufficiently standardized to admit of the searching comparison of the results of different observers. The present study, however, disclosed certain suggestive grounds for believing that the provocative Wassermann test is not merely another example of *post hoc, propter hoc*. Our conclusions are, therefore, carried to completion as if the worth of the test were fully established.

The material here presented consists of 103 cases in which provocative procedures to activate a negative Wassermann were undertaken for purposes of diagnosis. Parallel to this series, through the courtesy

of Dr. A. H. Sanford, we were given the opportunity to compare seventy-two repeated Wassermann reactions, done under conditions similar to those prevailing in the series of provocative tests. The work was not begun with any preconceived aim, but arose out of impressions developed in the course of the routine work of the Section, some of which have been confirmed and others reversed by the study. For that reason certain of the results show a mixture of methods, and represent the average conditions of a clinic rather than an experimentally controlled investigation.

In the provocative procedure, salvarsan or neosalvarsan alone, was used, no patients receiving mercury until the procedure was finished. The dosage varied from 0.3 gm. in the earlier cases to 0.6 gm. neosalvarsan or 0.4 gm. original salvarsan, in the later cases. The doses were varied with the conventional contraindications.

The negative Wassermann tests, as a result of which provocative procedures were carried out, were taken at varying intervals before injection, usually within a week. It was impossible usually to make repeated tests before injection. In a part of the series the blood to be tested for a provocative effect was drawn on the third or fourth, and the seventh days after injection. It had been our practice to perform the Wassermann tests on this blood on different days, thus introducing unintentionally the factor of technical variation to which Boas, King, and others have called attention. When it was definitely decided to make a study of a series, the procedure was modified in a limited number of cases, through the co-operation of Sanford, so that four different antigens were used for a time in the performance of these Wassermann tests, and so far as possible, the blood drawn just before injection and two or three of the bloods drawn after injection were run on the same day.

The routine Wassermann technic of the Clinic, carried out under the direction of Sanford, employs one Noguchi antigen and a rabbit-human hemolytic system, guinea pig complement and fresh, active patient's serum, with the usual controls. When more than one antigen was employed, two alcoholic extracts of syphilitic liver, a stock Noguchi antigen and an alcoholic antigen reinforced with 0.4 per cent cholesterin were employed. Two antigens adapted to other systems but tried out in the laboratory at this time were found to be anticomplementary in the dilutions used and the results discarded, which accounts for the gaps in the four-antigen series (Table I).

In common with a number of clinicians, one of us (Stokes) had been impressed with the provocative effect upon the Wassermann reaction of a single dose of salvarsan, by a case in private practice in which a Wassermann frankly negative by one serologist (using five antigens) and faintly positive by another, had become a two plus with one antigen forty-eight hours after injection of 0.3 gm. neosalvarsan, and three plus with two antigens seventy-two hours after injection, the second result being confirmed by a third serologist. The patient gave a positive history, and under treatment became entirely negative. Isolated examples of this type are probably fewer in number than they would be if a strict technic could be followed in all cases. In our experience in this series, the reversal of the Wassermann seems to occur rather abruptly in many cases, so that a twenty-four hour interval in drawing the blood is too long to get the finer gradations in intensity of the reaction which may be shown by very sensitive antigens. On the other hand, our series suggests that some of these finer gradations may be a function either of the technic or of variations in the behavior of the reagents, and for that reason must be interpreted with caution. We desire to add to the criteria already summarized by King, the opinion that a careful study of the results obtained by the serologist performing the tests is an integral part of the interpretation. Such an evaluation of the Wassermann furnishes interesting indirect evidence as to the existence or non-existence of provocative effects, even when the test itself as conventionally performed leaves uncertainties which impair its validity.

In estimating the trend of the Wassermann technic in accordance with this belief, we had available, through Sanford, the reports of seventy-two repeated Wassermann tests in untreated cases, each performed within the average period of time occupied by a provocative procedure and occurring among approximately six thousand tests. These had been requested by clinicians for the confirmation of the first finding, some as a matter of routine and others because the test seemed to conflict with clinical expectation, or, as in latent cases, came as a surprise to the clinician.

Of the 72 repeated tests, 25 (34.7 per cent) showed a reversal of the first finding by the second. Of these reversals, 3 (4.2 per cent) were from negative to positive (in the direction of the provocative) and 22 (30.5 per cent) were from positive to negative (against the provocative) including reversals from weak positive to negative. In

other words, the tendency of the Wassermann as carried out in the Clinic, was 30 in 100 against the production of provocative effects, as compared with 4 in 100 in the other direction, since in the former percentage of cases the mere repeating of the test was likely to convert even a previous positive into a negative, rather than the reverse. A variation of this type where a large number of Wassermans are being performed should be interpreted as an eminently conservative tendency which results in the production of more negatives than positives in suspected cases. Probably both factors are concerned, as shown by the analysis of the reversals by days. It may be stated in general, however, that it is the experience in the Mayo Clinic that the Wassermann as here performed is conservative, and is more likely to return negatives than positives in the face of a reasonable clinical expectation of syphilis.

Of the 25 reversals occurring on 15 pairs of days, 13 (52 per cent) could be grouped as occurring on 4 pairs of days. The percentage to be expected pro rata in these four days would be only 28.5. All these reversals were from positive to negative, so that none of them could have played the role of positive provocatives. On one of these days two weak and three strong positives were reversed to negative, and yet in spite of this apparently negative tendency on the second day, one provocative injection fell positive. On another pair of days, in which three reversals from positive to negative occurred, two provocative injections fell negative on the day of supposed negative tendencies. We were unable to find any evidence that on the days of supposedly positive tendencies, a tendency to produce positive provocative results occurred, but on one day of positive tendencies a Wassermann which had been positive three days before was reversed to negative. It seems evident from these figures that a number of factors are at work, in part inherent in the technic and reagents, as suggested by Haller's and Boas' results, and in part concerned with changes in the patient's serum as suggested by Craig. It seems fully as apparent that there is a variation in the technic of a competent serologist which must be a factor in provocative procedures undertaken with his co-operation. For that reason, as already stated, it is imperative in estimating the value of a provocative, that the trend of the serologist's technic should be thoroughly understood. It is Sanford's intention to do a Wassermann which will, if anything, err in returning negatives in syphilitics rather than positives in

TABLE I  
SUMMARY OF FIVE FOUR-ANTIGEN PROVOCATIVE TESTS

	Case 177785	Case 95838	Case 184981	Case 183729	Case 186777
Presalvarsan Wassermann	- 2/9/17*	- 2/27/17	- 2/9/17	- 1/23/17	- 2/27/17
Provocative injection	2/15/17** Neo, 5 gm. Intrav.	3/1/17 Neo, 6 gm. Intrav.	2/10/17 Neo, 6 gm. Intrav.	2/15/17 Neo, 6 gm. Intrav.	3/1/17 Old Sal. 3 gm. Intrav.
Antigen	I II III IV	I II III IV	I II III IV	I II III IV	I II III IV
First day	(M)† +++	- (M) +++	- - - - (H) +++	- - - - - - (M) +++	- - - - - - (M) +++
Second day	-	-	-	-	-
Third day	-	-	-	-	-
Fourth day	-	-	-	-	-
Fifth day	-	-	-	-	-
Sixth day	-	-	-	-	-
Seventh day	-	-	-	-	-
Eighth day	-	-	-	-	-
Ninth day	-	-	-	-	-
Tenth day	-	-	-	-	-
Eleventh day	-	-	-	-	-

\*Date of presalvarsan Wassermann.

\*\*Provocative injection with date.

†The (M) antigen is a cholesterolized alcoholic syphilitic liver antigen.

+++ indicates total inhibition.

†Results on Antigens C and K were discarded.

non-syphilitics; and his use of the less highly fortified antigens, the general experience of the Clinic with the Wassermann performed in his laboratories, together with the results of the examination described here, all entitle his technic to be regarded as conservative. The value of a reversal from negative to positive under a provocative procedure done with his cooperation is, therefore, entitled to correspondingly greater weight.

#### DIRECT EXAMINATION OF THE PROVOCATIVE PROCEDURE

Our efforts to satisfy ourselves of the existence of such a change in complement fixing power as the positive provocative Wassermann represents have not been entirely satisfactory, in that our conception of what constitutes rigid criteria was not reached until a number of results had accumulated, and the effort to try out the effect of a number of antigens and daily tests on the procedure overtaxed our facilities so that some confusion and partial results ensued. The occasions on which blood was drawn and tested just before the salvarsan was given and for several days after, all happened to be negative provocative tests, the results before and after salvarsan agreeing in being negative to all antigens used, when done on the same day. We are, therefore, left with the perplexing feeling that while there may be a provocative effect, and that a variety of considerations point to it, we have been unable to prove its existence beyond doubt with the facilities at our command. The demonstration of the value of the test can be made only by the use of methods which would be too elaborate to be applicable to average clinical conditions considering the amount of information which the test is likely to supply for purposes of diagnosis. The chief particular in which our more carefully worked out positive results do not conform to the strictest requirement is that pointed out by King, that the blood drawn just before salvarsan should be examined at the same time and with the same reagents as the blood drawn after it. Nevertheless, the five positive provocative tests represented in Table I are suggestive. The patient (Case 184981) in particular, exhibited in addition to his serologic changes, a local Herxheimer reaction in the grouped follicular recurrent syphilide of the buttock which he presented at the time of his examination. The lesions then healed, leaving scars. He gave a history of a genital lesion fourteen years before, no secondaries observed, local treatment only. The remaining

patients, except one, presented suspicious histories or findings which were not clear-cut.

Case 177785. Diagnosed clinically as pernicious anemia. Atypical as to blood findings and with central nervous system changes which suggested early tabes. He had given a weak positive Wassermann five weeks before the provocative, and a negative seven days before injection. The provocative effect outlined in the chart was followed by a negative six weeks later. A striking subjective improvement occurred, but should be interpreted with caution since only salvarsan was used, and the effect may have been due entirely to arsenic.

Case 95838. The wife of a syphilitic patient, anemic and below par. Husband with positive Wassermann had married her two years after an untreated infection. Aphonia lasting some weeks. Two negative Wassermans on previous occasions. Provocative effect followed by a complete negative on the ninth day, with a striking improvement under mercury.

Case 183729. Diplopia with right external rectus paralysis. History of gonorrhea from first husband. Two years later, transient diplopia; no symptoms during intervening time. Five years ago diplopia and strabismus reappeared and have been permanent; no other explanation than lues apparent. Spinal puncture not obtained. Nothing else on which to base a diagnosis of syphilis. The patient was negative as late as the tenth day after the one-antigen positives on the first and third days. No change under therapy. Clinically we regard this case as unconfirmed, though suspicious.

Case 186777. Definite history of old infection, with much treatment. Mental condition suggested an early paresis, but the neurologic findings were too indefinite on which to base a diagnosis. Puncture refused. No therapeutic test.

The antigen responsible for the majority of the positives above described was a cholesterinized alcoholic syphilitic liver antigen. This antigen, together with one of the stock acetone insoluble fraction antigens of the laboratory, had proved very sensitive in picking out suspicious cases which were negative to the ordinary technic. It remains a question in our minds, however, whether the possibility of false positives as suggested by such cases as No. 183729 is not too serious to discourage the interpretation of a positive with only one antigen in four as evidence of syphilis.

In only one of our series of nineteen positive provocatives done with



one antigen was there any evidence of a gradual increase in the strength of the complement fixing power of the serum, as evidenced by a weak, followed by a strong positive after salvarsan. In this case (Case 177564), a woman with gastric crises, a negative test four days before salvarsan was changed to a weak positive three days after, followed by a strong positive on the seventh day. Another patient (Case 179741) with early tabes, and a history of five injections of salvarsan and ten of a mercurial salt intramuscularly, was negative eight days before injection, weak positive on the sixth day after, and again negative on the ninth day. Cases of this type are merely suggestive, not conclusive, and as has been previously pointed out, form the basis for the doubts expressed as to the existence of a provocative effect because of their known occurrence under other circumstances. We feel, however, that the conservative tendency of the technic employed as evidenced in our comparative figures entitles such data to consideration in weighing the probabilities.

We believe that our direct data as presented herein, while not absolutely conclusive, offer strong presumptive evidence that a change in the complement binding power of negative syphilitic sera can be secured in a certain percentage of cases by the administration of an abrupt therapeutic shock, so to speak, in the form of an injection of salvarsan. The mechanism of such an effect can, in the present state of our knowledge of the immunology of syphilis, only be regarded as a matter for conjecture.

Granted then, for the time being, that a provocative effect exists, the following results may be presented as indicating the place which such a procedure should hold in the diagnosis of obscure syphilis. In considering the available material, data were gathered on relation of the provocative to clinical signs of syphilis, to the history of the disease, to the stage and type of syphilis, on the confirmation of the provocative test by the therapeutic test, and on the comparative value of the latter as a means of recognizing suspected cases. In estimating the efficiency of therapeutic tests, a liberal allowance was made for the recognized tonic effects of an arsenical preparation such as salvarsan, especially in conditions like suspected pernicious anemia, and the tuberculides, in which arsenic is known to be of value. It may not be out of place to state that for us a therapeutic test does not mean the administration of iodides, or the desultory or inefficient use of mercurials. Our average therapeutic test includes three weeks

of vigorous mercurialization with weekly injections of salvarsan if not contraindicated, the administration of the mercury being intramuscular, usually as a soluble salt, or by the vigorous use of inunctions.

#### THE POSITIVE PROVOCATIVE TEST

Of 103 provocative tests, 19 (18.4 per cent) showed a reversal of the Wassermann from negative to positive. This finding should be considered in the light of the comparisons with repeated Wassermans made above, in which it was suggested that the tendency of the technic to turn negatives into positives, unaided by a provocative injection, was only 4.2 per cent. If an injection of salvarsan can convert a 30.5 per cent tendency against a positive into an 18.4 per cent tendency in favor of a positive, it would seem to have a place as a diagnostic procedure.

Of the cases showing positive provocative tests, 26.3 per cent presented no objective clinical signs calculated to arouse the suspicion that the patient was syphilitic. Of the positive provocative cases, 73.7 per cent of the patients showed clinical signs which could be regarded as suspicious. In no one of the positive cases were the signs so indubitable that the provocative could be regarded as unnecessary or merely confirmatory. Typical examples of such groups of symptoms are found in sluggish pupils and indefinite gastric symptoms in the absence of definite stomach findings; periostitis of the sternum with enlargement of the liver, aphonia with slight anemia, etc.

A definite history of syphilis, interpreted to mean a reasonably clear account of primary and secondary manifestations, was given in 57.8 per cent of the positive provocative cases. Suspicious histories, such as miscarriages, infected husband, etc., were given in 31.5 per cent. No history whatever could be elicited in 10.7 per cent. In no instance was a provocative undertaken in the absence of both history and clinical signs.

The duration of infection ranged from one to eighteen years with an average of ten years. Two provocative tests were positive in patients giving a definite history of well treated infection but no signs where the test was intended to determine the need for further therapy. Since this constitutes a positive result in one-third of the cases in which we used the provocative procedure for this purpose, we believe the test has distinct value in determining the status of a patient under treatment. The Wassermann histories in general were unsatis-

factory. Four who gave histories of having previously been positive elsewhere became positive again after a negative in this Clinic.

The therapeutic test yielded figures of special interest, which it is our purpose to emphasize. Of the total number showing positive provocative effects, the therapeutic test confirmed the serologic finding in 60 per cent of fifteen patients that were treated. In 40 per cent the therapeutic was rated as doubtful or negative (6.7 per cent) and contributed nothing further to the diagnosis. The doubtful therapeutic tests included such cases as one patient with possible syphilitic anemia simulating pernicious anemia, treated with salvarsan, one with a history and previous antisyphilitic treatment but no signs, two undoubted syphilitics, one of whom had had so much recent treatment that little effect was to be expected, and the other so late and unfavorable that not much could be accomplished.

Previous treatment had been administered in 45 per cent of the patients showing a provocative effect, and 55 per cent had had no treatment. Two patients had been taking pills practically until their arrival. Of five who had had a fair combined treatment with mercury and salvarsan, three (60 per cent) were recognized only by the more sensitive antigens used. Two of these three were clinically suspicious, however, at the time.

The cases showing positive provocative effects were distributed as follows: Syphilis of the mucous membranes (late) 4 cases; of the skin, 3 cases; of the osseous system, 1; of the central nervous system, 3; of the vascular system, 1; latent cases, 4; type uncertain, 3.

#### THE NEGATIVE PROVOCATIVE TEST

Of the 103 provocative tests performed, eighty-four (81.6 per cent) showed no change in the negative Wassermann as the result of an injection of salvarsan. Of these eighty-four cases, 32.2 per cent were clinically negative, and 67.8 per cent clinically suspicious. It will be noticed that the tendency to a negative provocative is paralleled by fewer evidences of syphilis. Only 17.2 per cent of patients with negative provocatives gave definite histories of primary and secondary manifestations as compared with 57.8 per cent among the positive cases. In 52.6 per cent suspicious histories were obtained, a slightly larger proportion than among the positive cases. No suggestive history could be given by 30.2 per cent as compared with 10.7 per cent among the positive cases. The greater indefiniteness of history and

findings in the negative group, to be expected under the circumstances, is apparent.

The therapeutic test again affords interesting figures. Twenty-three patients received the benefit of a therapeutic test, and of this number, in spite of the failure of the provocative injection to reverse the negative Wassermann, 65.2 per cent showed improvement striking enough to clinch the diagnosis. This parallels the 60 per cent among the positive provocative cases, but is more significant because it made, instead of merely confirming, the diagnosis. In 34.8 per cent the negative result of the provocative test was confirmed by the absence of improvement under therapy. The therapeutic test was rated as doubtful in 13.3 per cent of the total number of negative provocative tests performed. A therapeutic test was advised in forty-three and carried out in twenty-three, or 53.5 per cent. In 51.2 per cent of the patients giving a negative result on provocative injection, the result was accepted as eliminating the possibility of syphilis in conjunction with the lack of definite findings. Cases of this type included histories of sexual exposure with neurotic and syphilophobic symptoms; selected cases of obscure arthritic manifestations without other evidence of syphilis; cases of epilepsy with one or two suggestive points in the family history but no stigmata; cases with histories of a previous positive Wassermann from unreliable source, without adequate clinical reason for suspecting syphilis; mental deviates and constitutionally subnormal persons presenting no definite stigmata of heredo-syphilis; patients with perforated nasal septum, with backache and negative x-ray; women with a series of miscarriages without other evidence of syphilis in history or examination; husbands or wives whose partners were syphilitic but who themselves presented no signs of the disease.

It is, of course, impossible to fit all types of cases into one rule in deciding the finality of a negative provocative procedure. It should be recalled that our fully developed technic called for five Wassermann tests over a period of from seven to ten days, so that in no case was a single negative accepted as evidence of the absence of syphilis. In many of the negative cases in which no therapeutic test was indicated, the patients were advised to repeat the Wassermann at the end of three months or more.

The cases in which no provocative effect could be secured included 1 of late syphilis of the mucous membranes, 2 of cutaneous late

syphilis, 4 of osseous syphilis, 9 of central nervous system involvement, 2 of vascular syphilis, two of heredo-syphilis, 6 latent cases and 58 which could be rated as so doubtful that a diagnosis of syphilis could not have been made without a positive Wassermann reaction. In only 13 per cent of the negative cases after a general examination did we feel that the diagnosis could be made clinically and that the provocative procedure requested by the general clinician was merely confirmatory.

## COMBINED RESULTS

Summarizing the results for our entire series, we find that 69 per cent or more than two-thirds of patients on whom provocative procedures were undertaken showed clinically suspicious signs of syphilis. A fourth of them (25.2 per cent) gave definite histories of primary and secondary lesions, half of them (48.4 per cent) presented suspicious facts in their histories, and the remaining fourth (26.4 per cent) could give no significant history. Two-thirds (63.1 per cent) of those treated (38 in 103) had their diagnosis made or confirmed by a therapeutic test, and two-thirds of these were from among those whose provocative test was negative, making therapy the last diagnostic resort (excluding in a small percentage, the possible results of lumbar puncture). Three-fourths of all the cases on which we had data (76) had been treated, one-fourth had not. The percentage of cases pre-

TABLE II

## SUMMARY OF CLINICAL RESULTS.

	Clinically suspicious %	Clinically negative %	Definite history %	Suspicious history %	Negative history %	Positive therapy %	Negative therapy %	Doubtful therapy %	Previous treatment %	No previous treatment %
Positive Provocative Effect	73.7	26.3	57.8	31.5	10.7	60.0	6.7	33.3	44.5	55.5
Negative Provocative Effect	67.8	32.2	17.2	52.6	30.2	65.2	34.8	—	32.8	67.2
Combined Results	68.9	31.1	25.2	48.4	26.4	63.1	23.6	13.3	39.4	60.6
Total Num- ber of Cases	103		95			38			76	

viously treated was, if anything, a little higher among those showing positive provocative effects than among those showing negative results (44.5 per cent as against 32.8 per cent). (Table II.)

With reference to the value of the provocative procedure in different types of syphilitic manifestations, Table III summarizes the results of our series.

TABLE III  
EFFICIENCY OF THE PROVOCATIVE TEST IN VARIOUS TYPES OF SYPHILIS

Type	Number of cases	Percentage positive
Heredo-syphilis	2	0
Osseous	5	20
Central nervous system	12	25
Vascular	3	33
Latent	10	40
Late cutaneous	5	60
Late mucous membrane	5	80

Combining certain of these results it appears that in only 27 per cent of cases is the provocative procedure likely to be of use in identifying active deep-seated visceral, osseous or central nervous system syphilis. Its efficiency rises to 40 per cent in latent cases, and to 70 per cent in late cutaneous and mucous membrane syphilis. It is in precisely these last mentioned types of syphilis that it is least likely to be of use, since the diagnosis can usually be made by a syphilologist from the morphology of the lesion. It appears, therefore, from our series, that the reactivation of a negative blood Wassermann for purposes of diagnosis is least valuable precisely where it is most needed; i.e., in obscure visceral, osseous and central nervous system syphilis. The number of cases is, of course, too small for final conclusions. We are unable to estimate accurately the possibility of false provocative results, since in three doubtful cases with positive results strong clinical ground still existed for suspecting syphilis, although the cases had to be left indeterminate.

#### DISCUSSION OF RESULTS

From our study of the provocative effect upon the Wassermann test, in clinical application, we feel that complete proof of the existence of such a reaction will be available only when the following technic has been carried out in a number of cases. Blood should be drawn at more frequent intervals than twenty-four hours—perhaps

as often as once in three or four hours—and one-half of it held in reserve to be done at a single sitting while the other half is examined day by day. Several antigens should be used, and these antigens and the other reagents employed should, so far as possible, be kept constant throughout the tests. A series of bloods should be examined before the provocative injection is given in order to ascertain, if possible, the normal behavior of the serum to be examined for provocative effects.

We have not been impressed with the necessity for continuing the examination of the blood after a provocative injection, beyond the tenth day. If possible, two serologists should work together, using the same reagents to determine the personal equation in the reaction. It is only necessary to total the figures for the number of single-antigen Wassermanns which would have to be done to satisfy these none too exacting requirements, to realize that the provocative Wassermann reaction will not soon rest upon an uncriticizable foundation.\* We had abundant reason to appreciate the almost insurmountable difficulties in the way of an absolutely controlled procedure, in the course of our own work.

The precise nature of the provocative effect, if such exists, could not be determined from our studies. We feel that there is reason to doubt whether it is comparable to the clinical Jarisch-Herxheimer reaction as suggested by our patient (Case 184981). Several of our patients who remained negative on the blood showed a symptomatic Herxheimer reaction. This was especially marked in patients with syphilitic periostitis, in which, after a marked exacerbation, the pain promptly disappeared. A local Herxheimer reaction was especially conspicuous in a periostitis of the upper third of the sternum (Case 185869) which, nevertheless, remained Wassermann negative, and cleared up subsequently under mercury and iodides.

\*Six bloods drawn in 24 hours on each case for 3 days— 18 single-antigen Wassermann tests.  
Two bloods drawn each 24 hours on each case for 7 days—

	14	"	"	"	"
Total	32	"	"	"	"
Dividing the blood for final and daily study	64	"	"	"	"
Dividing each blood between two serologists	128	"	"	"	"
Four antigens used on each case	512	"	"	"	"
Total	704	"	"	"	"

Our experience indicates that one case in five will furnish a positive effect. The investigator may, therefore, unless fortune favors him, have to provide for 2,560 single-antigen tests before securing one provocative effect completely worked out. This takes no account of the Wassermanns that should be done on the serum before provocative injections.

We were, in fact, impressed on several occasions with the value of the Herxheimer reaction as a corroborative sign, even when the provocative procedure had failed, and considered it an indication for a therapeutic test. Unfortunately, exact notes were not kept on this point, so that an estimate of its value will have to be deferred to a later study. Its value in syphilitic periostitis has been noted above.

The most interesting and suggestive result of the entire study to us, was the demonstration of the efficiency of the properly performed therapeutic test as a means of diagnosis in obscure syphilis, and its obvious superiority to the provocative procedure. We were also impressed by the parallelism between the percentage of patients who were clinically suspicious of syphilis (68.9 per cent) and the percentage proved to be syphilitic by an effective therapeutic test (63.1 per cent). It seems from these figures, as well as from the failure to secure provocative effects among cases in which there was serious doubt of the existence of an infection, that clinical signs are the basic fact in the diagnosis of syphilis. Their confirmation by therapeutic test was, in our series, greatly superior to an effort at diagnosis by provocative procedure. The efficiency of the provocative test in our series is approximately 18 per cent; that of the therapeutic test in the cases on which it was tried, was 60 per cent—a difference amounting to forty-two more chances in one hundred of clinching the diagnosis by therapy than by provocative. From our study of this series we should rate a thorough-going clinical examination first as a means of disclosing the presence of syphilis. A strong suspicion on examination, unconfirmed by Wassermann will have 18 per cent further prospect of confirmation by provocative, and the following of the negative provocative by a therapeutic test will give at least an additional 42 per cent prospect of identifying the trouble. Emphasis should be laid on the meaning of a clinical examination, which should include a careful taken history and the study of the patient at least from the point of view of the internist, the dermatologist, the ophthalmologist, the neurologist and the otolaryngologist before a final decision is reached.

In the foregoing presentation we have indicated in a negative way rather than a positive, what we regard as the indications for a provocative test and for subsequent application of a therapeutic test, by detailing the types of cases which were clinically doubtful with negative provocative tests. In general it may safely be said that



the provocative should not become a routine accessory of the negative Wassermann reaction in the absence of good clinical ground for suspecting syphilis, since the percentage of positives in such cases seems to be so small as not to justify the procedure.

While it is impossible to lay down the indications for a provocative procedure, and its limitations in cases in which it is most needed have been suggested in our results, we are accustomed to regard the following as indications, in addition to the more obviously clinical symptoms of the disease when occurring with a negative Wassermann:

1. A definite history of primary or secondary lesions or a suspicious genital sore of any description.
2. Syphilis in husband or wife or a history of a sore in either.
3. Treated cases to determine the fact of cure or need for further treatment. One-third of the cases thus tested by us, gave a positive provocative effect.
4. Obscure bone and joint lesions.
5. Histories of miscarriages unless the anatomical cause is glaringly obvious.
6. Mothers of syphilitic children without clinical signs of the disease.
7. Cases with a history of a positive Wassermann elsewhere, negative on present examination.
8. Mental deviates and constitutionally inferior individuals with suspicious histories.
9. Certain signs elicited by the special examinations, such as decreased bone conduction with normal hearing, chorioretinitis and retinitis pigmentosa, bilateral dacryocystitis in childhood, etc.

The technic of the provocative test, in our opinion, should include in practice, a Wassermann with several antigens done on blood drawn at the time of injection, and on blood drawn daily thereafter for one week. It is desirable that all these bloods be tested at one sitting, with the same reagents. This procedure is a serious tax on average clinical laboratory facilities, but we believe it offers the maximum prospect of success within the limits of clinical applicability. With the use of mercury intramuscularly as a provocative agent we have had relatively little experience, although we have

seen occasionally, apparently positive provocative effects secured by it. In a large clinic with a special service for syphilis, the salvarsan provocative is a so much more expeditious and compact procedure that it would seem the method of election wherever it can be used.

It is not our purpose in this paper to consider the technique and clinical applicability of the therapeutic test for diagnosis and the indications for its use further than to say that it should be conducted with vigor, tempered by good judgment, and not consist of iodides and pills. We are inclined to believe from our experience with it thus far that if it can be applied with the requisite judgment to properly selected cases it is so much more valuable than the provocative procedure that it should take precedence over it if a choice is necessary, and should follow it if the result of the provocative test is negative and the clinical suspicion strong.

#### SUMMARY

1. From a study of 103 cases in which an injection of salvarsan was given to provoke a positive Wassermann after a negative test, presumptive, but not conclusive evidence of the existence of a provocative effect was obtained.

2. A knowledge of the tendencies and limitations of the Wassermann technique employed should form a part of any study of the clinical value and interpretation of the provocative Wassermann test.

3. Such a study on a series of repeated Wassermann tests in the Mayo Clinic seemed to indicate that the tendency of the technique was conservative and against the conversion of negative into positive reaction without the administration of salvarsan.

4. It seems probable that both individual technical variations and variations in the reagents are a factor in the results in addition to the provocative effect.

5. Positive provocative effects were obtained in 18.4 per cent of 103 cases.

6. The provocative test was of value in recognizing as insufficiently treated, two out of six cases (33.3 per cent) in which it was applied to determine whether a cure had been attained.

7. A strictly controlled and completely worked out provocative procedure involves an amount of labor which makes it clinically inapplicable, and it seems probable that this same obstacle will keep it

in the field of presumptive rather than conclusively demonstrated clinical phenomena for some time to come.

8. The provocative test in our series seemed to be of the least service in active deep seated visceral, osseous and central nervous system syphilis, where it was most needed, fairly efficient (40 per cent) in latent syphilis, and most often positive in late cutaneous and mucous membrane manifestations, where the diagnosis can often be made morphologically.

9. Our results do not suggest that the provocative is entirely a Herxheimer reaction phenomenon, since local and symptomatic Herxheimer reactions occurred in our series in cases in which no provocative effect could be recognized, as well as in cases showing a provocative effect. It is possible, however, that the use of several very sensitive antigens might demonstrate an effect not detected in routine procedure.

10. A suggested procedure for provocative tests is given on page 645 and seems to us to represent a compromise between the clinical impossibility of a fully controlled procedure, on the one hand, and partial and untrustworthy methods on the other. At its best the test yields a rather small return for the amount of trouble, and if over-elaborate, is subject to the same risk of error as the over-sensitive Wassermann test.

11. Certain special indications for the provocative procedure are enumerated on page 645.

12. The percentage of cases whose syphilis was suspected from clinical examination ran parallel to the percentage shown to be syphilitic by therapeutic test, and far in advance of the number shown to be syphilitic by the provocative test.

13. The therapeutic test, properly applied to suitable cases, would seem to be of more value in clinical diagnosis of obscure syphilis than the provocative Wassermann test.

14. Positive therapeutic effects were obtained in 63.1 per cent of thirty-eight cases, and in 65.2 per cent of twenty-three cases in which the provocative test had failed to establish the presence of syphilis.

15. The provocative Wassermann would seem to be of little value in the absence of clinical evidence of the disease, and to be in-

ferior both to clinical judgment and the therapeutic test in the recognition of obscure cases.

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## CASES OF HYPERTROPHIC CIRRHOSIS OF THE LIVER\*

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CIRRHOSIS of the liver, by which is meant hepatic sclerosis, or fibrosis, is a condition which results from one or more of many causes. These causes are often indicated in the nomenclature, as, for instance, *alcoholic cirrhosis* and *syphilitic cirrhosis*. Often, however, the causes are obscure and hence the nomenclature becomes more general, as, for instance, in *atrophic cirrhosis*, *hypertrophic cirrhosis*, and the like. Under certain circumstances a symptom complex appears which is characterized anatomically by an atrophic liver, and other associated phenomena, physical and anatomical, which make up the picture of what we know as Laennec's cirrhosis. Under other circumstances a different complex appears which is known as Hanot's cirrhosis. In the latter, the essential anatomic lesion is hypertrophy and fibrosis of the liver. Standing close to this latter there is a large group of cases in which the liver is enlarged, often to a severe degree, but in which certain of the characteristics of Hanot's cirrhosis are absent. These are the plain undesignated hypertrophic cirrhoses, the causes of which are not known unless perhaps it is true that lues is an important etiologic factor in them. What the relation is between these two groups of cases, in both of which the liver is large and fibrotic, is a question. One sometimes thinks that they vary clinically merely because of the direction the cellular changes take. In one case the biliary system may be predominantly though secondarily damaged, while in another, the vascular system receives the brunt of the attack. In one group the infection may be hematogenic, following the hepatic or portal systems. In the other, it is ascending, i. e., biliary.

However that may be, it will be interesting to compare the following three cases, in all of which the essential and apparently primary lesion was an enlarged liver.

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## CASE I

M. O., Hospital No. 4957, a married white woman 45 years of age, was admitted to the Cincinnati General Hospital on September 27, 1915, complaining of weakness and jaundice.

*Family History.*—Her mother died at 77 of "paralysis." One sister died of "typhoid fever." The husband died of tuberculosis seven years ago, after an illness of six months duration.

*Past History.*—The patient had measles, whooping cough and chicken pox when a child. She denied typhoid or malaria. Four years ago she was operated upon twice for the removal of necrotic bone from the ankle. She has had a nasal polyp removed, and three years ago had a tumor removed from the uterus. Eight years ago she had two attacks of jaundice each of which lasted about 2 weeks. With neither attack did she complain of pain or of chills. For the past few years she has been drinking heavily. Menstruation was always regular until 3 years ago (operation for uterine tumor), since which time there has been no flow. There is no history of hemorrhoids. She was married nine years ago. She has one child 20 years old and healthy. She has had no miscarriages.

*Present Illness.*—This began a week before admission with weakness and jaundice, feverishness and chills. For three days she has been in bed. For two days she had sharp pains in the liver region radiating to the right shoulder. She vomited twice during this time.

*Present State.*—The patient is a well developed and nourished white woman, who appears weak and stupid. Temperature 102; pulse 130; respirations 40. The conjunctivæ are icteric. The nose, ears and neck are negative. The tongue has a white coat. The gums are pyorrheic. Nothing noticeable is discovered in the breasts, lungs, or heart. The pulse has a fair quality, and is regular and rapid. The abdomen is not distended, but there is tenderness in the right hypochondrium, with which is associated a slight rigidity of the right rectus, and some enlargement of the liver. (The grade of enlargement is not given.) No other essential data appear in the records of the physical examination.

Later, on the day of admission, the patient complained of joint pains, but none of the joints appeared to be swollen or tender.

September 28. The patient complained of weakness. Stools clay color. Urine highly colored. There were a few purpuric areas on the fingers. Temperature 99.6; pulse 100; respirations 26.

September 29. The temperature varied between 99.8° and 103.6°; pulse 124; respirations 40. Examination of the chest was negative. The patient has not rested well, the jaundice is intensified, and the body is covered with a petechial eruption. The liver dullness seems to be increasing. The patient has had periods of delirium during the day. The tenderness and rigidity of the upper right abdomen persists.

September 30. The temperature has ranged from normal to 101.6°; pulse 100; respirations 24. Because of extreme restlessness in the early morning, the patient was given chloral, and later morphia and hyoscin. The urine contains bile, albumin and granular casts. The liver dullness reaches to just below the

level of the umbilicus. There is increased abdominal rigidity and tenderness. Operation, suggested to a brother, was refused.

October 1. The jaundice is slightly intensified, and there is some pain in the joints of the arms, particularly in the left elbow. Temperature 99.2° to 100°.

October 2. Temperature 100.2° to 104.2°. Pulse 92-120; respirations 24. The patient is extremely restless at night, and complains of severe pain and tenderness in the left elbow. The arm was put in an L splint. At times she is delirious. The liver dullness remains the same; the stools are clay color. Urination is involuntary.

October 3. Temperature 98.4°-104.2°; pulse 112; respirations 9-24. Urine shows bile, and a trace of albumin.

October 4. Temperature normal; pulse 92; respirations 16. The jaundice is decidedly intensified. The petechial hemorrhages are more evident. The liver dullness is stationary. The breath sounds in the left back are roughened but not bronchial in character. There are no râles. The patient is rational and voids freely. Petechial hemorrhages, 2-3 mm. in diameter, are distributed over the whole body.

October 5. Temperature 97.8°-100.4°. General appearance, as to jaundice and petechiæ, the same. Is occasionally delirious. Was given 1000 c.c. of Fischer's solution intravenously. Three hours later all the dressings were saturated with blood. Five hours after the wound was dressed, the dressings were again blood-soaked. The wound was exposed, the sutures removed and the wound explored. No cause was found for the hemorrhage.

October 6. The urine remains acid and contains albumin. Submucous hemorrhages are present in the mouth and on the lips, and the jaundice is intensified. The petechial eruption has subsided but not disappeared.

There is no further note. Death occurred on October 7.

*Clinical Diagnosis.*—Suppurative cholangitis; chronic alcoholism; chronic interstitial nephritis.

#### AUTOPSY PROTOCOL

The body was that of a gray-haired, well built, well nourished, woman—5' 2" in height. The pupils were contracted. The whole surface of the body was brilliantly icteric, and scattered over it here and there were numerous small superficial hemorrhages. Larger purpuric lesions were present over the upper portion of the left thigh, where there was a band of edema and hemorrhage, 8 cm. wide, parallel to Poupart's ligament and extending from below the anterior superior spine to the inner anterior aspect of the thigh. On the right arm externally, over the middle of the triceps, was an irregular area of hemorrhage. Another existed in the bend of the elbow. Over the flexor tendons of the right ankle was a large atrophic stellate scar; 4 cm. below the umbilicus was an atrophic scar 9 cm. long which had been the result of a surgical incision. There was a severe pyorrhea. The peripheral lymph glands were not perceptibly enlarged; and were firm and shotty. There was no edema and no joint enlargements.

When the body was opened, the lungs collapsed. The intestines lay in their

normal position. The appendix was present and healthy. The uterus and ovaries were absent. The omentum was exceedingly fatty, as was also the mesentery. The subcutaneous fat was increased in amount and the muscles were of good color, though yellowish. All the connective tissues were deeply stained with yellow. There were no nodules in the mammary glands. The mediastinum contained increased fat. There was no evidence of thymus remains. There was no increase of pericardial fluid.

The left lung was removed with no difficulty except that caused by a small mass of fibrous adhesions which united the lateral portion of the upper lobe with the parietal pleura. In each lung were a few scattered fibrous and calcified nodules. Besides these there was no evidence of tuberculosis. The posterior portions of both lungs were congested and edematous, and this hypostatic condition was best developed in the lower lobes. Both upper lobes were moderately moist but contained air. There were no areas of consolidation. The heart was small and flabby. It was bile-stained and showed an increase of epicardial fat. Except for these things and the presence of four pulmonary cusps, there was nothing remarkable. The tips of the papillary muscles were fibrotic, and the attachments of the aortic valves were sclerotic, but there was no evidence of any serious cardiac difficulty. The orifices were not dilated. The aorta, save for the bile staining and a few scattered patches of fatty degeneration with no gross atheroma, was smooth and healthy. The spleen was large and soft. The edges were thick and rounded. The whole surface was distinctly reddened with small petechial hemorrhages and was covered with the tags of fine recent fibrinous adhesions, and a still more recent fibrinous exudate. On section, the pulp was soft and edematous, and a clear dark, slightly brownish-red. The Malpighian follicles were not enlarged. The organ showed a general increase in fibrous tissue, as shown by resistance to cutting.

The liver was very large (3235 grams). As it lay in the body, the left lobe was just visible beneath the costal margin, while in the right mammillary line, the edge of the right lobe lay 10 cm. below the costal margin. The notch was directly under the ensiform, and was filled with a solid, elastic nodular mass as large as a bantam egg. Beneath this, and just to the right, was the small gall bladder, containing a single small, irregular, almost black stone. The surface of the liver was generally of a greenish color with markings of yellow. It was marked by a number of contracted stellate scars which ran down into the substance of the organ. Section of the nodule from the hilus showed a mass of pale, hyaline tissue with no evidence of caseation though there were yellowish streaks across it. In its periphery were a few spicules of calcified material. The whole appearance was that of a large gumma completely replacing a lymph gland. It was in a position to exert pressure upon the hepatic duct which, however, was patent. The cystic and common ducts were patent. The papilla of Vater was buried in the intensely edematous mucous membrane of the duodenum. The cut surface of the liver was generally greenish in color, mottled with yellow. It showed fibrous strands running from superficial stellate scars, and a moderately increased glissonian tissue about the portal vessels. There were no gross evidences of gummata or abscesses.

The kidneys (left 200, right 190) were soft and juicy. Upon each, the capsule



was slightly adherent, but stripped with comparative ease leaving a moderately finely granular, occasionally torn, pale, yellowish surface, marked with exceedingly numerous petechial hemorrhages. The cortex was thickened beyond the normal and the line of demarcation was faint. The whole cut surface (especially the cortex) was marked with fine hemorrhages, and in the pelvis was a small amount of brownish, muddy urine. The ureters and bladder were not abnormal.

The pancreas was buried in a mass of fat and on section gave evidence, in the resistance to cutting, of fibrosis. The cut surface was, for the most part, pale, with a few scattered small hemorrhages. Extending into the gland from the periphery, were strands of fatty tissue. The stomach showed a moderately well marked Russian leather appearance with no rugæ, and a considerable mucous covering. There were many subserous hemorrhages in the course of the intestinal tract and many in the mesentery and omentum.

*Anatomic Diagnosis.*—Hypertrophic (biliary cirrhosis); gummatous hepatic lymphadenitis; acute catarrhal duodenitis; chronic catarrhal gastritis; chronic diffuse nephritis; acute nephritis; cholelithiasis; fibrosis and fatty infiltration of the pancreas; myocardial fibrosis; obsolescent pulmonary tuberculosis; icterus; purpura; acute splenic tumor; terminal septicemia.

Cultures from the spleen showed a pure growth of streptococcus mucosus (W. B. W.)

#### REMARKS

In this case there are two possible etiologic factors upon which one can put his fingers.—alcohol and lues. The former is definite; the latter, suggested by the history, and borne out by the autopsy. It is possible that another infection than lues may have been a factor, and that this accounted for what were probably attacks of catarrhal jaundice. The case offers a good example of a terminal septicemia.

#### CASE II

M. K., Hospital No. 192047, a white man 45 years of age, was admitted to the Cincinnati General Hospital on January 31, 1915, complaining of a "very bad cold and weakness."

The *family history* was not obtained except that there was no history of tuberculosis or cancer.

*Past History.*—Seventeen years ago the patient had typhoid and three years later gonorrhea. Otherwise the history was negative.

The *present illness* commenced three weeks before admission with an acute attack of cough and general malaise. Despite these, the patient continued to work for two weeks. At the end of this period he became very weak and at the end of the day his feet were swollen. The appetite remained good.

*Present Condition.*—The patient was a fairly well developed and well nourished white man. The skin was jaundiced. The eyes were normal; the scleræ were yellow. The ears and nose and throat were negative. The breath was foul, the teeth fair, the gums pyorrheic, and the tongue raw looking and clean. The cer-

vical glands were not enlarged. The chest was well shaped and the expansion even. The area of cardiac dullness was normal, and the heart sounds were clear. The lungs were negative. In the epigastrium was a slight bulging over which the percussion note was flat. There was no tenderness. Beneath the surface was a mass with an even hard border and not notched. The flatness was continuous with that of the liver, and did not extend upward beyond the area of normal liver dullness. It was distinct from the area of splenic dullness. The spleen was not palpable.

February 1. The icterus has deepened. The epigastric flatness is unchanged. The stools are clay colored and contain some fat. There is a trace of bile in the urine. Leucocytes 12,800 per c.mm.

February 2. A stool contained some dark clotted blood. The urine contains bile. The patient feels well.

February 3. A slight rise of temperature.

February 12. Two slight attacks of epistaxis. Jaundice increased.

March 1. Jaundice increased. Area of liver dullness enlarged. Stools dark brown. Urine negative except for a trace of bile. Patient feels bad.

March 5. Leucocytes, 13,500 per c.mm.

March 8. Transferred to surgical service.

March 9. Leucocytes, 16,000 per c.mm.

March 11. Cholecystostomy performed.

March 14. General condition good, except for slight cough.

March 15. General condition worse. Abdomen distended and tympanitic. Temperature not high. Hiccoughs. "Percussion and auscultation shows presence of hypostatic pneumonia."

March 16. Condition worse. Patient very weak. Died at 8:30 p.m.

*Clinical Diagnosis.*—Hypertrophic cirrhosis.

#### AUTOPSY PROTOCOL

The body of an emaciated, intensely jaundiced man of apparently 50 years of age, and apparently a foreigner. He had a scant black beard and scant black hair. From the mouth, a thin, blackish, almost coffee-ground material oozed. Below the right costal marginal was the wound of a recent surgical operation from which a red rubber tube projected. From the tube there was no flow. The wound was healing well by primary intention about the tube. There was no suppuration about the sutures. Beneath the skin on either side of the wound, the muscles and subcutaneous tissues were filled with blood which was not completely coagulated. The skin over the cecum was beginning to show postmortem discoloration. There was no edema. The peripheral lymph glands were not enlarged. The entire surface of the body was markedly icteric with a bronze tint. The conjunctivæ and mucous membranes were yellow. Scattered here and there, particularly along the right side and flank, but also over the thorax, were numerous petechiæ, or occasionally vibices. In the left axilla was a subcutaneous hemorrhagic suffusion, the result of three needle punctures (intravenous). Rigor

mortis was present. Postmortem lividity was evident. The head was not opened. The drainage tube was firmly in place in the contracted remains of the gall bladder, and in its lower part was a thick, greenish-stained mucoid material. When the body was opened, the lungs did not collapse. The stomach appeared hugely dilated, and in this dilatation, the duodenum participated and to a less extent the small bowel. The cecum was very much dilated. The appendix was normal.

In the right pleural cavity, there were numerous recent fibrinous adhesions over the upper and lower lobes laterally and anteriorly. In the left pleural cavity there were old fibroid adhesions anteriorly over the upper lobes and posteriorly over the lower. The left lung showed a considerable degree of edema, though crepitation was present. The anterior two-thirds of the right middle lobe and the adjacent parts of the upper lobe were completely noncrepitant and consolidated. On section, the consolidated areas were gray and granular but rather juicy and stickier than in the typical lobar pneumonia. Microscopic examination showed capsulated diplococci and streptococci. The heart was not enlarged. There was no hypertrophy of the walls, the myocardium was gray, the valves apparently normal, and the endocardium smooth. The aorta showed nothing but a few patches of fatty accumulation beneath the intima. The spleen weighed 185 grams. It was distinctly cloudy and pale. The resistance to cutting was perhaps a trifle decreased, and the follicles slightly increased in size. The kidneys were of the same, approximately normal, size, and exceedingly pale. The cortices and medulla showed a normal relationship. The pelves were clear. The ureters were apparently normal.

The liver weighed 1945 grams. It was exceedingly pale, and stained a general diffuse greenish yellow. Especially about the edges, it showed also lacey markings of deep green. The consistence was markedly increased. The lobules were visible. The cut surface showed the same general appearance as the surface. The gall bladder had been opened and drained, and from it was projecting a drainage tube, held firmly in place by sutures. About it loops of small and large intestine, and the omentum were collected and adherent by recent fibrinous adhesions. There was no evidence of infection. The bile ducts were patent and easily permitted the passage of a small probe. The hepatic ducts and the pancreatic were also patent and the duct of Santorini also was normal. About the head of the pancreas was a group of very firm, pale lymph glands. Frozen sections of these showed only fibrosis.

The stomach was hugely dilated and filled with a blackish, sour-smelling, almost coffee-ground material. The same sort of fluid was present in the duodenum. The mucous membrane of the stomach was pale and smooth except for numbers of small submucous hemorrhages. There was nothing abnormal, other than the dilatation of the small bowel. The large bowel was small and contained a semi-fluid, grayish-brown material. The pancreas was apparently normal. The adrenals showed no abnormality. The bladder and prostate were not unusual.

*Anatomic Diagnosis.*—Hypertrophic hepatic cirrhosis; acute septic lobar pneumonia; acute (toxic) diffuse nephrosis; acute fibrinous pleuritis; acute dilatation of the stomach; icterus; anemia, cholecystotomy.

## REMARKS

In this case the factor of infection is present, as in Case I. In it, however, there is no evidence of lues except that suggested by the fact that the patient had had gonorrhea. The evidence points to the probability that the active infection, which accounted for the leucocytosis, was terminal and not the cause of the cirrhosis.

## CASE III

L. W., Hospital No. A-1854, a white woman, 29 years old, was admitted to the Cincinnati General Hospital on March 14, 1916.

(The following note appeared at the head of the history sheet. "The history is not very reliable for it was obtained from a negro with whom the woman has been living.")

About the middle of last July, the patient had a miscarriage at about the third month. During the following December, the regular menstrual period was much prolonged and bleeding was profuse. In January the hemorrhage recurred and lasted three weeks. There has been no hemorrhage since. In December there was some swelling of the feet and legs. Since January, the patient has vomited a good deal. She has complained of pain in the abdomen and of feeling ill since the first of the year. Her appetite has been poor. She has been drinking a great deal of whiskey—from one to two quarts a day. She will drink all the whiskey she can get, and has done this for a good many years. During the last three or four months she has lost a great deal of weight. She has never been jaundiced before. During this attack she has been confined to bed for three or four weeks before admission to the hospital, but was able to get up for a short time until two weeks before admission. She has eaten nothing but has been able to drink whiskey.

*Present State.*—The patient is deeply jaundiced, and quite dyspneic. The mouth is open and dry. The patient is very stuporous and does not complain of pain. The skin over the entire body is intensely yellow. The pupils are pinpoint in size and do not react to light nor during accommodation. The conjunctivæ and scleræ are yellow. One cornea (the right) seems dry and reddened. There is a mucous discharge up on the conjunctivæ. The teeth are in very bad condition and are covered with a brownish-black debris. The lips are dry and parched. The gums are reddened and pyorrhæic. The tongue is dry and heavily coated, as is also the roof of the mouth, with a dry brownish material. The throat is not seen. The breath is foul. The cervical glands can not be felt, and there is no enlargement of the thyroid.

As the patient lies on her back in bed, the left side of the chest is higher than the right. Over the lower chest the veins are distended and prominent. On percussion the note seems a little higher pitched beneath the right clavicle. Beneath the left clavicle and in both axillæ there is moderate hyperresonance. Over the left base and in the axillary line the note seems to be abnormally high pitched. On auscultation the breath sounds, though harsh, are clear, and expiration is pro-

longed over the fronts and sides. No rales are heard. The lower lung border is at the fifth rib in the midclavicular line. The point of maximum cardiac impulse is neither seen nor felt. Relative cardiac dullness extends 4 cm. to the right in the 4th interspace, 10.5 cm. to the left in the 5th interspace, and above to the 3rd rib. The heart sounds are weak. At the apex the first sound is louder than the second. No murmurs are heard. At the base the pulmonic second is accentuated and is much louder than the aortic second. In the aortic area the sounds can scarcely be heard. There are no audible murmurs. Splenic dullness extends from the 7th rib in the midaxillary line to the costal margin. The median border can not be felt or detected by percussion. On auscultation of the chest, the breath sounds are clear and strong but expiration is prolonged over the apices and interseapular space. The breath sounds are a little distant over the right base.

The abdomen is distended evenly with the apex at the umbilicus about 2.5 cm. to 3 cm. above the level of the ribs. The veins, especially those on the right side, are distended, and are visibly continuous with those of the lower thorax. On palpation, a mass can be felt in the abdomen. This extends from the costal margins down almost to the pelvis on the right, and about 3 cm. to the left of the umbilicus. The mass is hard, and the border feels fairly sharp and well defined along the median edge, and almost below. A little above and about the level of the navel there is a small movable mass measuring 2 to 2.5 cm. and seemingly situated in the abdominal wall. It feels like a gland. The edge of the large mass does not feel very irregular, and the whole mass moves up and down with respiration. Its position corresponds with that of the right lobe of the liver. The left lobe of the liver is four fingerbreadths below the costal margin. The percussion note over the mass and in the right flank is dull. Over the left side of the abdomen and flank there is tympany. There is a moderate edema of the abdominal wall. There are no excoriations anywhere.

There is no swelling of the legs. The knee jerks are present. Babinski, Oppenheim and Chadwick signs are absent. There are no scars on the skins. The radial pulse is weak and thready.

*Vaginal Examination.*—There is a profuse yellowish vaginal discharge, some reddening of the mucous membranes, and a moderate grade of prolapse. The cervix points forward, is fixed, and feels rather firm and irregular.

*Rectal Examination.*—There are no external hemorrhoids. The sphincters seem normal. No masses are felt.

The urine is dark greenish-brown, and contains no albumin (heat and nitric acid) or sugar. There are fairly numerous granular casts, a few leucocytes, and many red cells.

Blood pressure. Systolic 88; diastolic 64.

A leucocytic count was not made but from the smears there seemed to be a leucocytosis. A differential count of 200 cells gave lymphocytes 9 per cent; large mononuclears, 1.5 per cent; transitionals, 6 per cent; polynuclears, 82.5 per cent; eosinophiles, 0.5 per cent; no mast cells.

A second examination when the patient was not quite so distended, showed an abdominal mass, rounded below, and four fingerbreadths beneath the left costal

margin, which might correspond to the left lobe of the liver or to the spleen. It is continuous with the splenic dullness in the axillary line.

The impression received at this time was that the case was one of hypertrophic cirrhosis with enlargement of the spleen.

March 17. The patient is continuously in a semistuporous state, and occasionally shrieks. The temperature and pulse have risen slightly but rather steadily since admission and the temperature has been between 100 to 101 since March 16. Urination and defecation are involuntary. Both discharges are bile stained. Pelvic examination. The cervix is filled with a greenish-yellow discharge. There is a small tear in the lower part of the cervix.

March 22. The patient has been gradually sinking. The corneæ have become ulcerated. The discharge from the eyes is increased. The pulse is barely perceptible. Smears from the cervical discharge show no gonococci. The urine contains albumin with small granular casts, blood, and pus cells. Blood cultures remained sterile. A Wassermann test was positive only with cholesterinized antigen.

The patient died on March 22.

*Clinical Diagnosis.*—Hypertrophic cirrhosis; chronic nephritis; hypertrophy and dilatation of the heart; congestion of the lungs, liver, spleen, and kidneys; vaginitis; cervicitis; keratitis; syphilis.

#### REMARKS (R. S. M.)

The age of the patient is somewhat against carcinoma. The size and surface feeling of the liver are rather characteristic of hypertrophic cirrhosis. The nodule felt to the left of the navel is, however, suggestive of a metastasis. The negative pelvic examination together with the absence of other than the possible single metastasis, throw doubt upon the probability of cancer. From the history of alcoholism, one might expect cirrhotic changes in the liver together with chronic diffuse nephritis. The lack of emaciation is against malignant disease. Hypertrophic cirrhosis is more common in males. Except for the nodules, hypertrophic cirrhosis would seem to explain the enlargement of the liver, with jaundice, better than any other condition.

#### AUTOPSY PROTOCOL

The body was that of a slightly built, well nourished young woman of about 30 years of age. The general color of the body was a brilliant yellow orange. Rigor mortis was present; lividity was present but not brilliant. There was a slight edema of the legs. The peripheral lymph glands were not appreciably enlarged. The teeth were in an exceedingly bad condition. The gums were retracted and pyorrheic. Upon the lips were thin, dark brown crusts. The right pupil was irregular, the iris narrowest toward the inner canthus. On the inner side of the cornea was a small area of opacity which seemed to be superficially

ulcerated. The right pupil was small and contracted, and immediately above it, extending toward the inner canthus, was a distinct corneal ulcer  $1\frac{1}{2}$  cm. in length which had almost perforated. Upon the eyelids there was a small yellow dried purulent secretion. All of the mucous membranes were deep yellow. The finger nails were pale. In the bend of the left elbow were the puncture wounds caused by hypodermic medication. Over the lower part of the sternum there were groups of cutaneous ecchymotic hemorrhages and scattered over the upper part of the chest there were some scattered patches of diffuse reddish subcutaneous hemorrhage. There were scattered echymoses on the thighs and just above the pubis. Over the sacrum was a shallow bed sore. Just below the right knee internally was a hypertrophic linear scar, 3 cm. long. The lower margin of the liver was 16 cm. below the tip of the ensiform and 15 cm. below the costal margin of the mammillary line. The subcutaneous fat was well developed and of the same color as the skin. The muscles were distinctly pale and rather dry in appearance. The omentum was coiled up upon the left lobe of the liver above the transverse colon. The appendix was present and apparently healthy. The visceral peritoneum was smooth and slightly congested. There was one small strangulated appendix epiploica on the sigmoid. There were no abnormal adhesions between the intestinal loops and no obvious abnormality of position of the intestines.

When the sternum was removed, the lungs did not collapse. There was no fluid and there were no adhesions in either pleural cavity except in the left where there was one small band of fibrous adhesions between the lower lobe and the diaphragm posteriorly. The mesenteric fat was very well developed. The whole peritoneum had somewhat of a grayish-green color. About the spleen there were numerous old adhesions binding it to the diaphragm and to the stomach.

The liver was enormously increased in size, (4380 grams), the increase being especially noticeable in the right lobe. The greenish-yellow surface was mottled with fine paler clearer yellow spots and was generally smooth, but upon the surface of the left lobe there were two scars both of which showed contraction, and in this contraction, the liver substance beneath was involved. Both scars were rather rounded and had the form of smooth craters. In the right lobe of the liver just beside the falciform ligament and almost at the notch, was a larger, more irregular scar over which the capsule was more thickened and beneath which the liver was more distorted. On the lower edge of the left lobe was still a more distinct, larger, rather smooth, crater-shaped scar with a tendency to stellate contraction. On cross section, there was a general light olive green color to the parenchyma, which color showed a distinctly lobular arrangement. About the lobules there was a much paler color. There were a few small nodules of clear yellow. The general consistence of the organ was decreased, and there was a very evident increase in fat in the organ. Small globules of fat were seen in the fluid on the cut surface.

The right lung was small and boggy. There was no evidence of pleural adhesions and the pleura was generally smooth. It was crepitant throughout though the crepitation was decreased. Posteriorly there was evidence of hypostatic congestion. The apex was scarred. On section, the parenchyma showed merely a moderate grade of congestion with some edema and all of the connective tissues

were shown as distinctly yellow bands. The whole organ had a carnified feel. The left lung was rather more voluminous than the right. The surface was smooth except on the diaphragmatic surface where there was less evidence of hypostasis, and the color was somewhat paler. The apex was not scarred. Beneath the pleura were one or two small obsolescent tubercules. Cross section showed evidence merely of moderate degree of edema.

There was an increase of perirenal fat. The adrenals were apparently atrophic both as to their medullæ and cortices. There was less lipoid change than was usual. Cavitation was beginning. The right kidney (160 gm.) was of about normal size, perhaps slightly decreased in size. The capsule removed with fair ease but tore the surface at occasional places. The organ was distinctly adematous and deeply jaundiced. In the papillæ were some evidences of fibrosis. The cortex, however, was of about normal thickness and the relation between cortex and medulla was normal. The glomeruli could be seen as small congested points. The line of demarkation between cortex and medulla was lost. The stellate veins were injected but not particularly congested. The left kidney was slightly larger, (160 grams), than the right, but had the same general characteristics and appearance. There was no obvious difference on inspection.

The heart was of normal size. The tricuspid orifice admitted 3+ fingers. The right auricle was slightly dilated. The whole heart was flabby and jaundiced. The pulmonary orifice appeared normal. There were no thrombi in the auricular appendages. The left auricle was small as was also the left ventricle. There was a rather diffuse thickening of the epicardium over the left ventricle. The mitral valve was somewhat thickened on the edges. The chordæ tendineæ were sclerotic and rather contracted. The papillary muscles were distinctly fibrotic. The aortic valves were apparently healthy. There was some slight evidence of adhesions between the various cusps at their points of attachment, but there was no other macroscopic evidence of disease. The aorta, except for a few patches of fatty degeneration just above the aortic valves, and except for the intense jaundice that extended throughout the aorta, was macroscopically normal. The myocardium was pale and in it one could see patches of fibrosis stained yellow. The coronaries were evidently not sclerotic nor tortuous.

The spleen was large, exceedingly soft and flabby. The capsule was marked with tags of old adhesions but was otherwise thin and approximately normal in appearance. The pulp was exceedingly soft, almost diffuent and could be expressed from the trabeculæ. The Malpighian bodies were just visible on the pulpy surface. (Cultures were negative.)

Between the body of the uterus and the left ovary there was considerable sclerosis and scarring of the pelvic peritoneum which had caused a certain amount of kinking of the left tube. In this mass of fibrous tissue the ovary was buried. From the fimbriated extremity of the left tube a small amount of a distinctly yellowish pus could be expressed. The bladder was almost completely filled with a dark brownish-red clot. The mucous membrane of the bladder was congested, rather diffusely but particularly so in the region of the trigone and just to the left of the left ureter was an area of ecchymosis which may possibly have represented the origin of the blood clot. The vagina was deeply pigmented so that it



was of a distinctly green color with some hemorrhage. The cervix was lacerated and contained a mucopurulent fluid around which there was a small amount of grumous material. The body of the uterus was firm, the endometrium was congested but not obviously unhealthy.

The stomach was small and contracted. The tips of the rugæ were diffusely congested. There was an increase in the amount of mucus upon the mucous membrane of the stomach. Upon stretching the organ, the rugæ did not disappear completely. The duodenum showed a certain amount of increased catarrhal exudate upon the surface, otherwise was not especially abnormal. The bile ducts were patent.

The pancreas was small and congested, but showed no macroscopic abnormality.

The intestines, neither large nor small, showed any obvious abnormality. There was no enlargement of Peyer's patches and the solitary follicles were not enlarged. The mucous membrane had a generally slaty greenish color, most marked in the middle portion of the jejunum and in the colon.

*Anatomic Diagnosis.*—Hypertrophic cirrhosis; myocardial fibrosis; edema of the lungs; chronic diffuse nephritis (parenchymatous type); cervical erosion; ulceration endocervicitis; acute splenic tumor; jaundice, anemia; acute bilateral keratitis; syphilis; iritis.

#### REMARKS

In this case, the luetic factor seems more prominent than in either of the previous cases. In it is also the possibility of an alcoholic etiology. Which of the two is the more important, can only be surmised.

#### SUMMARY

Three cases of hypertrophic cirrhosis of the liver are reported. In all of them there is a suspicion of lues. In two there was a definite evidence of lues. In all there was a probability of alcoholism. In two there was a definite history of alcoholism. In two, the age was 45; in one, 29. In the latter the largest liver was encountered (4380 grams).

The three cases are summarized as follows:

Case I. A woman, 45 years old. History of recurrent attacks of jaundice, alcoholism, and irregular sexual relations. No miscarriages. Just before admission a history of fever and chills, jaundice, pain in the hepatic region radiating to right shoulder, and vomiting. Physical examination disclosed pyorrhea, abdominal rigidity, enlarged liver (below the umbilicus), joint pains, clay colored stools, and bile stained urine. Autopsy showed an enlarged jaundiced liver (3235 grams), an enlarged spleen, a gumma of a lymph gland, stellate hepatic scars, cholelithiasis, pancreatic fibrosis, and septicemia.

Case II. A man, 45 years old. History of typhoid and gonorrhea. Onset with cough and weakness. On admission was jaundiced. Physical examination showed pyorrhea, enlarged liver, clay-colored stools, leucocytosis. Later, there was blood in the stools, but no bile, and epistaxis. A cholecystostomy was done after which death followed from postoperative pneumonia. Autopsy showed cutaneous hemorrhages, a liver weighing 1949 grams, a spleen weighing 185 grams, hyperplastic pancreatic lymph glands, and a septic pneumonia (diplococci and streptococci).

Case III. A woman, 29 years old. History of menstrual disturbances, irregular sexual relations, and of alcoholism. On admission was deeply jaundiced and dyspneic. Gums pyorrheic. Superficial veins of thorax and abdomen distended. Liver enlarged. Spleen palpable. Purulent vaginal discharge. Leucocytosis. Corneal ulceration. Blood culture negative. Wassermann positive. Autopsy showed a large jaundiced liver (4380 grams), in which were contractile scars; large spleen. Spleen cultures were negative. Myocardial fibrosis; endocervicitis and purulent salpingitis.

# LEUTIN REACTION IN CARDIO-VASCULAR-RENAL DISEASES

## REPORT OF THIRTY-THREE CASES

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OWING to the possible erroneous impression which might be produced by such observations as those of Stoll<sup>1</sup> and Hanes<sup>2</sup> regarding the frequency of a positive luetin reaction in nephritis, we thought it might be of interest to report our observations upon the following subjects having vascular or vasculo-renal disease.

So far as could be ascertained, none of these patients had had for several months, or were having during observation, potassium iodide. The technic used in these cases was the usual one—.06 to .08 c.c. of luetin was injected intracutaneously in the outer surface of the arm. The point of injection was observed daily for three days and every other day for six days longer. A papule the size of a split pea or a pustule was considered positive.

In this series of twenty-two cases of nephritis and one arteriosclerotic kidney, there were eleven Wassermann reactions done, but one of which was positive. In this one, the luetin test was negative. The luetin tests were negative except in two cases—one of which had a negative Wassermann, the other having none.

In the four cases in which there was a diffuse dilatation of the ascending aorta, of the arch, or of both, as diagnosed by physical examination and the x-ray, there was but one positive Wassermann reaction and two positive luetin reactions, one of which was present in the patient having the positive Wassermann.

## SUMMARY AND CONCLUSION

We did luetin tests upon twenty-eight patients suffering from cardio-renal-vascular diseases who, as nearly as could be ascertained, had had no potassium iodide for several weeks, at least. Eighteen

<sup>1</sup>Stoll, H. F.: *Am. Jour. Med. Sc.*, 1915, cl, 178.

<sup>2</sup>Hanes, F. M.: *Am. Jour. Med. Sc.*, 1915, cl, 703.

Name	Age	Systolic Blood Pressure	Diastolic Blood Pressure	Diagnosis	Syphilitic History	Wass. Reaction	Luetin Reaction
W.	59	200	120	Chr. Inter. Nephritis Hemorrhagic Retinitis	Neg.	Neg.	Neg.
W.	45	170	110	Chr. Inter. Nephritis Detached Retina	Neg.	Neg.	Neg.
W.	51	130		Chr. Inter. Nephritis	Neg.	Neg.	Neg.
O.	46	200	140	Chr. Inter. Nephritis	Neg.	Neg.	Neg.
McL.	54	170	95	Chr. Inter. Nephritis	—	Neg.	Pos.
J.				Chr. Inter. Nephritis	—	Neg.	Neg.
R.	67	205	100	Chr. Inter. Nephritis	—	Neg.	Neg.
H.	67	205	80	Chr. Inter. Nephritis	—	Neg.	Neg.
B.	56			Chr. Inter. Nephritis	—	Neg.	Neg.
R.	50	105	70	Chr. Inter. Nephritis	—	Neg.	Neg.
R.	46	190	150	Chr. Inter. Nephritis	Pos.	—	Neg.
R.	28	160	100	Chr. Inter. Nephritis	Neg.	Neg.	Neg.
A.	62			Chr. Inter. Nephritis	Neg.	Neg.	Neg.
C.	50	160	90	Chr. Inter. Nephritis	Neg.		Neg.
A.	72			Chr. Inter. Nephritis	Neg.	Neg.	Neg.
W.	65	240	130	Chr. Inter. Nephritis	—	Neg.	Neg.
L.	68			Chr. Inter. Nephritis	Neg.	Pos.	Neg.
M.	72	140	65	Chr. Inter. Nephritis	—	Neg.	Neg.
H.	34	240	130	Chr. Inter. Nephritis	—	Neg.	Neg.
H.	29	200	118	Chr. Paren. Nephritis	Neg.	Pos.	Pos.
C.	54	110	75	Chr. Paren. Nephritis	Neg.	Neg.	Neg.
S.	24	120	80	Chr. Paren. Nephritis	Neg.	Neg.	Neg.
S.	63			Arteriosclerotic Kidney	Neg.	Neg.	Neg.
B.	62	130	90	Diffuse Dil. Aorta	Pos.	—	Pos.
P.	43	125	80	Diffuse Dil. Aorta	Neg.	Neg.	Neg.
S.	57	120	80	Diffuse Dil. Aorta	Neg.	Neg.	Neg.
McL.	26	120	70	Diffuse Dil. Aorta	Neg.	?	Pos.
O.	43	195	135	Hypertension	Neg.	Neg.	Neg.

of the patients had Wassermann reactions, but two being positive. Of these twenty-eight, four had positive luetin reactions; and of these four, but one had a positive Wassermann.

In our short series, we are led to believe that either the luetin reaction is unreliable, or syphilis is not a common etiological factor in these conditions.

## A NOTE ON THE TREATMENT OF SYPHILIS WITH GALYL

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**D**URING the past seven years, salvarsan and its substitutes have taken a permanent place in the therapy of syphilis. By the administration literally of millions of doses of salvarsan, no doubt of its efficacy in all stages of syphilis exists, and the modern physician would no more think of treating a case of syphilis without it than he would of treating a case of diphtheria without antitoxin.

Salvarsan, however, is a patented preparation, and as there have been times during the past two years and a half that this product has not been available in this country, reliance in the treatment of syphilis has been placed on one or another of its substitutes. Therefore, when new substitutes for salvarsan appear, which bear the stamp of approval of eminent syphilologists, it seems desirable to give them a fair trial, especially if these products can be marketed cheaper than salvarsan, or if any claims to superiority over the latter drug are made.

One of these substitutes which has received but scant notice in this country, but which seems to deserve a better acquaintance, is galyl. This drug was discovered by Mouneyrat, of Paris, and was named galyl after Galan, who first noted the properties of arsenic. Galyl, or tetraoxydiphosphaminodiarsenobenzine, is a yellow or grayish-yellow powder, containing 35.3 per cent arsenic and 7.2 per cent phosphorus. It is odorless, tasteless and insoluble in water, alcohol, ether and benzene. It is, however, readily soluble in a dilute solution of sodium carbonate, forming a yellow or yellowish brown liquid. The ampules in which galyl is dispensed contain a small quantity of sodium carbonate so that solution takes place readily upon the addition of distilled water. It is, therefore, as easily prepared for injection as neosalvarsan.

Like its prototypes, salvarsan and neosalvarsan, galyl has been administered subcutaneously and intramuscularly, but owing to the pain and occasional necrosis, these methods have been abandoned with this drug also, and intravenous method is the one of choice.

According to the majority of workers who have employed galyl, it is at least as efficacious as salvarsan or neosalvarsan, and most investigators state that it is less toxic.

Thus, Beurmann, Mouneyrat and Tanon<sup>1</sup> assert that the tolerance for galyl is greater than for any of the other arsenical compounds, which have, up to the present, been administered intravenously. Bruner<sup>2</sup> states that it is less toxic than salvarsan.

Foerster<sup>3</sup> reported nine cases of active syphilis injected with galyl and reached the conclusion that it is superior to salvarsan and neosalvarsan with regard to its effect upon so-called primary and secondary lesions.

Others who have reported favorably upon galyl are Spence,<sup>4</sup> Dudley,<sup>5</sup> Troisfontaines,<sup>6</sup> and Thomson.<sup>7</sup>

My experience with galyl has been limited to sixty injections administered to twenty-eight patients and on account of the small number of injections, definite conclusions can not be drawn; therefore the object of this note is not to report upon its use, but merely to bring it to the attention of the profession. I should like to say, however, that the results with galyl seem to be as good as with other arsenicals and in my limited experience there have been absolutely no untoward symptoms following its injection.

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<sup>1</sup>Beurmann, Mouneyrat and Tanon: Bull. et mém. Soc. méd. d. hôp. de Paris, Jan. 24, 1913.

<sup>2</sup>Bruner: Am. Med., July, 1914.

<sup>3</sup>Foerster: Lancet, London, Sept. 18, 1915.

<sup>4</sup>Spence: Ibid., Dec. 11, 1915.

<sup>5</sup>Dudley: Ibid., July 8, 1916.

<sup>7</sup>Thomson: The Medical Officer, Aug. 5, 1916.

<sup>6</sup>Troisfontaines: Presse méd., Nov. 1, 1913.

# Abstract of Current Syphilis Literature

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WM. H. DEADERICK, M.D., EDITOR

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SYPHILIS, A DISEASE OF DIMINISHING SEVERITY.—Douglas Symmers, New York, Social Hygiene, 1917, vol. iii, p. 203.

There was a time when syphilis was an exceedingly vicious disease attended by extensive destructive changes in various organs resulting in rapid death. Latter-day syphilis, on the contrary, is essentially a disease of slow evolution, marking its progress by years rather than by weeks or months, and is attended by changes in the body that are comparatively mild and limited in extent. Thus, post mortem statistics affirm that less than 7 per cent of the bodies reveal anatomical indications of syphilis, while in the living patient the Wassermann reaction is positive in over 25 per cent of all persons investigated. The difference is striking, and justifies the deduction that many individuals become infected by syphilis without sustaining bodily injuries of a detectable nature. At the same time it is a noteworthy fact that, of all syphilitic lesions encountered at autopsy, a large percentage involves organs of negligible importance so far as life is concerned, and that even syphilitic changes in such tissues as the heart, brain and lungs, are often compatible with life. Clinical observations carried over a long period of years, and studies in the immunity of syphilis, furnish highly suggestive evidence in support of the view that mankind is extensively, if not uniformly, syphilized in greater or less degree, and that, in future generations, the process will become progressively milder and ultimately assume a place among diseases of negligible intensity.

IMMUNOLOGICAL STUDIES ON PURE CULTURES OF VARIOUS SPIROCHETES.—Hideyo Noguchi and Seinai Akatsu, New York. The Journal of Experimental Medicine, 1917, vol. xxv, p. 765.

Experiments were carried out for the study of culture spirochetes in their relation to various immunity reactions *in vitro*. Several strains of *Treponema pallidum* and one each of *Treponema calligyrum*, *Spirocheta refringens*, *Treponema microdentium*, and *Treponema*

*mucosum* were used. Tests were made for immune substances responsible for agglutination, complement fixation, spirocheticidosis and opsonization. In cases of agglutination and complement fixation, cross titrations were made. In the sera derived from rabbits immunized with various spirochetes, agglutinins were demonstrated in varying quantities for the homologous antigens. The amounts of agglutinins developed were considerably higher in the *pallidum* immune sera than in the other groups. There was no parallelism between the amounts of antigens injected and the amounts of agglutinins developed. Cross titrations among different *pallidum* strains revealed that the agglutination is not necessarily strongest when homologous antigens and immune sera are brought together. On the other hand, the reactions between the immune sera and antigens belonging to different species were sufficiently specific to justify the grouping. Certain degrees of group reaction were observed between the *pallidum* immune sera and the *calligyrum*, and occasionally very faintly also between the *pallidum* and the *refringens* antigens and *vice versa*. There was a much more pronounced group reaction between the *calligyrum* and *refringens*. The immune serum and antigen of the *microdentium* showed a slight affinity for the *mucosum* but none for the *pallidum*, *calligyrum*, or *refringens* while the *mucosum* immune serum caused a slight agglutination with many members of the other groups. Hence, it appears that the *pallidum* is more or less related to the *calligyrum*, while the affinity between the *calligyrum* and *refringens*, and possibly also between the *calligyrum* and *mucosum* in a much smaller degree, seems close. The *microdentium* showed the least relation to any other spirochetes. Titration of agglutinins in the sera obtained three months after the cessation of immunization revealed that the agglutinin contents were already greatly reduced, having fallen roughly to 0.01 of the original strength. The rates of disappearance were irregular in different animals and bore no direct relation to the initial titers. Titration made of the immune sera which had been preserved aseptically in a refrigerator (6° C.) during the same period (three months) indicated that the original strength of these sera was reduced to about one-tenth. The agglutinins disappear from the rabbit's body much more rapidly than they are reduced in the separated sera by deterioration on standing at 6° C. Titration of the immune sera for complement fixation power showed with a few exceptions, in which there was only slight complement binding, that the titers were high enough to indicate the presence of this principle. The *antipallidum* sera possessed higher average titers than the other immune sera tested with correspondingly homologous antigens. The least active were the *antirefringens* sera. Cross titration of *antipallidum* immune sera for complement fixation showed that a given serum with a high titer for its own strain of antigen was also strong with most of the other strains of the *pallidum*. Instances occurred



also in which the titers with heterologous *pallidum* antigens fell far below those of the homologous. Group reactions between the different spirochetes, such as the *pallidum* and the *calligyrum*, the *calligyrum* and the *refringens*, and the *microdentium* and the *mucosum* were also indicated. The *mucosum* and the *pallidum* showed a slight degree of group reaction. No *antipallidum* serum fixed complement with the *microdentium*. The immune sera were tested for their spirocheticidal properties *in vitro* against the correspondingly specific and heterologous varieties and without the addition of complement. Many of the *antipallidum* sera killed their own strains. Normal rabbit serum exhibited only a slight degree of inhibition. Without complement, the immune sera caused a considerable reduction in the number or density of colonies, but not a complete suppression of growth. Complement alone had no injurious effects upon the *pallidum* strains. The antisera for the *calligyrum*, *refringens*, and *mucosum* showed feeble spirocheticidal action, while the antisera for *microdentium* was stronger. A syphilitic rabbit serum tested against a strain of culture *pallidum* gave a feeble inhibitory effect. Under the influence of immune sera and complement, the spirochetes undergo within a few hours complete disintegration or granular degeneration. Without complement, they are more powerfully agglutinated, but no disintegration occurs, even after 20 hours, and complement alone has no effect. In the presence of homologous immune serum and complement, the culture *pallidum* may be ingested by the leucocytes, but phagocytosis is slight, possibly on account of the filamentous nature of the organisms. The spirochetes in such a mixture disintegrate within a few hours, disintegration being especially rapid when the immune leucocytes are used. In the absence of immune serum, phagocytosis is not noticeable, while without complement but in the presence of immune serum and leucocytes, some phagocytosis, without subsequent lysis, occurs. A virulent strain of *pallidum*, obtained from syphilitic orchitis in a rabbit, exposed to agglutination, lysis, and phagocytosis by an immune serum prepared by means of culture *pallidum* strains, showed only slight agglutination and phagocytosis but rapid immobilization without disintegration in the presence of complement.

THE ANNULAR MACULAR SYPHILIDE, OR SO-CALLED NEURO-SYPHILIDE.  
—Howard Fox, New York. The Journal of Cutaneous Diseases,  
1917, vol. xxv, p. 215.

The eruption differs from the ordinary early macular syphilide in that the lesions are fewer in number and invariably larger in size. They form circles and portions of circles and at times, by coalescence, large polycyclic figures, the largest lesions being observed during the later period of the disease. It seems to be

generally agreed that the macules do not spread in a serpiginous manner but appear as circles and remain as such without change until influenced by treatment. The color of the lesion is described as being at first a bright red, with a tendency after a time to assume a yellowish tone. The color also varies with changes of temperature. In the stage of retrogression a certain amount of pigmentation is present. Scaling is almost entirely absent. In a few cases, a very fine desquamation has been noted, chiefly at the time of involution of the lesions. The sites of predilection of the eruption include the flexor surfaces of the forearms, the buttocks and sacral region and the abdomen and thighs. It is conspicuous by its absence on the face and neck, where the annular papular syphilide is so often seen. Most of the cases reported were seen in young adults who, as a rule, were in excellent physical condition. The annular syphilide has a decided tendency to recur even when a liberal amount of treatment has been given. It may occur two, three, or even four times.

TWO CASES OF PROBABLE SYPHILIS OF THE INTESTINES.—D. A. Haller and I. C. Walker, Boston, Mass. *The American Journal of the Medical Sciences*, 1917, vol. cliii, p. 824.

Case 1. White male aged 32 years. In the summer of 1916 he developed a bloody diarrhea, averaging ten or twelve bowel movements daily. These were very loose and were mixed with dark blood at times. At various times he passed pure blood alone with small strings of mucous membrane with the blood. The present attack began six months ago and was similar to previous attacks except that it was more severe. In the last two weeks he lost ten pounds in weight. The physical signs appeared negative except that the epitrochlear, cervical inguinal glands are palpable and that in the lower right quadrant of the abdomen the individual loops of intestines are easily made out through the belly wall and are slightly tender to firm pressure. Urine was negative, leucocytes were 13200, eosinophiles five per cent, Wassermann reaction was four plus positive. Spinal fluid showed two cells per c.mm.; globulin negative, Fehling's test negative; stool examination showed blood mixed with mucus, but no amebæ tubercular bacilli, ova or parasites. Guaiac test was strongly positive. The bismuth roentgen ray examination showed no evidence of gastric or duodenal ulcer; some ileal and cecal stasis, a bismuth residue in the ileum after nine hours and in the cecum after thirty hours. The mucous membrane of the rectum is definitely hyperemic and there is a surface coating of bloody purulent mucus which can be wiped off, leaving a granular looking surface epithelium which shows evidence of some superficial

desquamation. There are no discrete circumscribed ulcers made out, but there are numerous small hemorrhages in the mucous membrane. Apparently the rectal wall is thicker, firmer and more rigid than normal, and gives one the impression of a leathery consistency. After antisyphilitic treatment there was marked improvement. Being readmitted about eight months later his former trouble had reappeared and after further vigorous antisyphilitic treatment he was entirely cured.

Case 2. Negro male aged 29 years. Two weeks ago he suddenly became nauseated and vomited. There was no pain. During the next few days he vomited once or twice. Three days after the first attack he had a colicky pain in the epigastrium. After a few days of rest from work he resumed his labors again, the vomiting returned and vomitus was black in color. The epitrocleas, cervicals and inguinals are palpable. There is slight tenderness on palpation in the epigastrium. Reflexes are not obtained on either side; Wassermann four plus; there are eight lymphocytes in the spinal fluid per c.mm. and the spinal fluid Wassermann is negative. Stools are dark and tarry and contain mucous. The x-ray of the abdomen indicated ileal stasis, the larger part of the residue being in the distended colon and the sigmoid very redundant. Diarsenol and intramuscular injections of mercury and potassium iodides were begun. Four days after the first dose of diarsenol all pain and vomiting ceased and in ten days he had gained 3.5kg.

SYPHILITIC FEVER IN RELATION TO GYNECOLOGICAL AND OBSTETRICAL PRACTICES.—Fred J. Taussig, St. Louis. *Surgery, Gynecology and Obstetrics*, Sept., 1916, p. 274.

The diagnosis of syphilitic fever can rarely be made with absolute certainty, but we should more often consider it as a possibility, and institute antiluetic measures in suitable cases. Secondary syphilitic fever occurs in a mild form in 20 per cent of patients at the outbreak of the rash and at times is prolonged and more severe in its course. Late secondary syphilitic fever is occasionally seen in a pronounced form after confinement or in gynecological patients. Tertiary syphilitic fever is practically never due to syphilitic lesions in the female genital tract. One such case is reported by the author. It may, however, complicate a gynecological or obstetrical condition and, owing to the difficulty in locating the site of the tertiary lesion, lead to a wrong diagnosis as to the cause of the fever. All doubtful cases should be subjected to a Wassermann test and, if possible, given antiluetic treatment. Syphilitic fever is probably due to the reaction of the body to the toxins produced by the spirochetes

which under certain circumstances or in certain individuals gain an entrance into the circulation.

**THE RELATION BETWEEN DIABETES MELLITUS AND CLINICAL SYPHILIS.**—Jacob Rosenbloom, Pittsburgh. *The Journal of the American Medical Association*, 1917, vol. lxviii, p. 1232.

Of the sixty-two cases of diabetes mellitus studied, there is positive evidence of syphilis in seven, or 10.3 per cent. Five of these seven patients were persuaded to take syphilitic treatment. There was no increase in tolerance for carbohydrate in any of these cases after treatment. On this account, it cannot be stated definitely that the diabetes was due to syphilis. It is, however, logical to think that they exist as independent conditions, at least in the cases that are presented in this paper.

**CARDIAC SYPHILIS.**—Thomas E. Satterthwaite, New York. *Therapeutic Gazette*, January 15, 1917.

A diagnosis at the present day should be based upon a previous history of syphilis, often in a patient who has been treated by the regulation methods of former times, with mercurials and the iodides, until no visible, palpable, or subjective signs of the disease have remained. In fact, it may have lain dormant ten, twenty or even thirty years. The most distinctive diagnostic signs are arteriosclerosis; a weak, arrhythmic pulse, frequent or infrequent; dilated heart, angina, aortic dilation, or aneurism; valvular disease, usually aortic; finally, the Wassermann or other luetic reaction. The results of therapeutics afford most valuable aid in diagnosis. The discovery of the spirochete pallida has not only revolutionized our previous knowledge of syphilis, but has made our diagnosis, prognosis and treatment more effective. Not only is syphilis a more common disease than was suspected, but in a certain number of cases it is the actual cause of death from heart implications. The prognosis is bad, but not altogether so. If the diagnosis can be made early, and the proper treatment instituted and maintained wherever any indication of the disease is apparent, some success may be expected. Even in advanced cases, where, for example, there is tabes dorsalis, improvement can sometimes be effected. Yet notwithstanding that we may be able to remove the deposits by medicine, usually a something will remain, so that if the part resumes its psychological activity, it still may not be sound pathologically. Cardiac syphilis is more common than has been supposed. Like syphilis of the lungs, it exists, and the physician who fails to appreciate either of them falls short of his duties as a practitioner of medi-

cine. In fact, neither heart nor lungs should be examined without always holding in view the possibility of syphilis as the cause of the disease. Where it may not be possible to make a positive diagnosis, a probable one can be reached. Appropriate treatment will confirm it. Cardiac syphilis is an insidious disease, and its manifestations are neither pronounced nor distinctive. A cure may be possible, while relief is probable, if the lesion is not too far advanced. If in such cases the physician fails to recognize the existence of syphilis, he should not be surprised if his patient is carried off without warning, by sudden heart failure. Treatment consists in the use of salvarsan, the iodides, and mercurials, and if there has been a positive Wassermann, it should be continued until a negative is obtained. Afterwards the treatment should be along the line of therapeusis in other cardiac affections. It must, however, be borne in mind that there are some dangers connected with the use of salvarsan, especially if injected intravenously.

**SYPHILIS OF THE STOMACH.**—Paul Rockey, Portland, Ore. *Northwest Medicine*, 1917, vol. xvi, p. 103.

Efforts to estimate either the absolute frequency of gastric syphilis, or its frequency relative to other gastric conditions, must be obviously uncertain, considering the number and character of collected reports. In syphilitics with gastric complaints, where the cause is not in the stomach, it may be due to syphilis of organs in relation, as liver, pancreas, lymph nodes; to perigastric adhesions of syphilitic origin; to reflexes from syphilitic lesions at more distant points in the abdomen; to the toxemia and cachexia of the disease, as happens in pulmonary tuberculosis and in malignant disease elsewhere than in the stomach; and to specific lesion in the brain; or to the gastric crises and gastric symptoms of tabes. Apparently syphilis of the stomach occurs in the tertiary stage or occasionally late secondary. Grossly, syphilis may affect any part of the stomach wall, as gumma, infiltration and ulcer. It seems reasonable to suppose that carcinoma may develop in a syphilitic ulcer. The therapeutic test, when used, should be adequate. Response to it will probably be definite, but there are cases of syphilis unusually resistant to antiluetic treatment. There are nonsyphilitic dyspepsias that may be benefited for a time by antispecific treatment. The prognosis of luetic gastric ulcer, untreated, would presumably be worse than that of simple ulcer, but if treated probably as good or better.

ICTERUS GRAVIS SYPHILITICUS; ITS RELATION TO ACUTE YELLOW ATROPHY.—Udo J. Wile and Rolla G. Karshner, Ann Arbor, Mich. The Journal of the American Medical Association, 1917, vol. lxxiii, p. 1311.

Jaundice in early syphilis is now recognized as occurring in two forms, mild jaundice and severe jaundice, or icterus gravis. The mild form, which is by far the most common, differs very little in symptomatology from ordinary catarrhal jaundice. Of far greater importance than mild icterus is the grave form, which often supervenes on the former, though it may rise insidiously with a stormy onset and rapid course. The tendency if untreated, is for the condition to go on to acute yellow atrophy. The symptomatology of icterus gravis is that of acute yellow atrophy, differing chiefly in the fact that it yields to specific treatment when recognized early. The onset is variable, generally insidious. A mild icterus usually appears as the first objective sign, occasionally accompanied by malaise, vomiting and constipation, but usually without gastrointestinal symptoms. There may be a slight rise in temperature, though subnormal temperatures are often reported. The pulse is slightly accelerated. Severe abdominal pain may be complained of. Lumbago and muscular pain are common. There is often a debility similar to that of typhoid fever. This may go on to collapse. Cases are reported with ascites. While not a uniform finding, hemorrhagic symptoms are mentioned by many authors. These are manifested by gingivitis, bloody vomits, melena, purpuric spots on the skin, hematuria and metorrhagia. There is often a hemorrhagic nephritis. Pregnant women may abort, but this is not always the case. The second stage is very definite in onset and is marked by a pronounced change for the worse in the general condition, by rapid decrease in the size of the liver, the occurrence of leucin and tyrosin in the urine and especially by the appearance of nervous symptoms. Headache appears which, if present before, becomes very intense. There may be pupillary disturbances and amblyopia. Mentality is affected. The patient may become depressed, or restlessness may supervene during which there are insomnia, pain, convulsions and delirium. The patient often screams and becomes very violent. Apart from the jaundice, the clinical symptoms may closely resemble meningitis. The urine is diminished in amount and highly colored with bile pigment. There is no glycosuria. Small amounts of albumin often occur together with casts. Albumosuria is reported and is supposed by some to come from direct destruction of the liver cells. Crystals of leucin and tyrosin are invariably present in greater or less amounts, often in so great an abundance that they spontaneously precipitate. In

some cases the stools contain bile pigment; in others they are clay colored.

VISCERAL LESIONS IN LATENT SYPHILIS. (Lantern Slide Demonstration).—Aldred S. Warthin, Ann Arbor, Mich., Mississippi Valley Medical Journal, 1917, vol. xxiv, p. 124.

The material presented represents one hundred and sixty-five autopsies upon bodies showing the lesions of a generalized syphilitic infection. In but a small number of these was the existence of syphilis positively known clinically; the majority came from the clinic of internal medicine, as cases of nephritis, heart disease, etc., without suspicion of the true nature of the affection. In over fifty of these cases, without any clinical history of syphilitic infection or of symptoms of this disease, and with negative Wassermann reactions, the spirochetes of syphilis were demonstrated in the tissue lesions. The general pathologic pictures in these undiagnosed cases is precisely the same as in the cases in which syphilis had been recognized. Several cases of paresis were included in this list. The general pathology of the cases of paresis is identical in kind with that found in the myocardial, nephritis, and other forms of latent syphilis. The pathology of these varied clinical types of latent syphilis varies only in localization and degree. The syphilitic nature of these lesions has not hitherto been recognized, and the discovery of the relationship of the spirochete to these lesions has enormously broadened our conception of this disease. The myocardial lesions occur in every case of syphilis, recognized or unrecognized, treated or untreated, cured or uncured. Active lesions have always been found when a sufficient time has been given to the search. In every case of latent syphilis the author also found active lesions in the aorta. The gross appearance of aortic syphilis may or may not resemble those formerly taught as diagnostic of syphilitic aortitis. Cases in which the old classical picture of syphilitic aortitis is seen in the gross always show active lesions in abundance microscopically, but other cases in which the aorta presents the typical picture of a senile atherosclerosis may also show microscopically active lesions of syphilis and spirochetes. Likewise in all of the author's cases of latent syphilis the pancreas shows a more or less marked fibrosis. Similar infiltrations of plasma cells with slight fibroblastic proliferation occur in the liver, around the portal vessels; in the capsule and medulla of the adrenals; in the testis, with atrophy of the germinal epithelium and a slow progressive hyaline fibrosis of the tubules; in the adventitia, and perivascular tissues of the mesenteric and prevertebral blood vessels; in the meninges, in the brain and cord, in the intestinal and stomach

wall, in fact, around any blood vessel anywhere in the body there may be localization of spirochetes with the production of these small inflammatory lesions.

CONJUGAL TABES DORSALIS.—T. B. Throckmorton, Des Moines, Iowa. *Journal of the American Medical Association*, 1917, vol. lxviii, p. 1389.

A man aged 66 years, complaining chiefly of urinary incontinence, inability to walk properly, periodic attacks of pain involving the trunk and lower extremities dating back twelve or thirteen years. Examination of the nervous system revealed marked ataxia of both the upper and lower extremities. The right pupil was larger than the left one and was irregular in outline. The Argyll-Robertson phenomenon was present. The knee and ankle jerks were absent, the upper reflexes remaining intact. The Wassermann reaction was weakly positive. A lumbar puncture was refused. Several months after the first examination a perforating ulcer made its appearance on the plantar surface of the right foot at the base of the great toe. A year later death ensued. The posterior columns of the cord, especially in the lumbar and lower dorsal segment, were greatly atrophied; and cross sections revealed, even to the naked eye, a flattening and shrunken appearance of the dorsal columns. The wife, aged 56, denied any primary or secondary symptoms of syphilis. At the age of 51 she began to have vague pains in the lower extremities. Unsteadiness of gait, diplopia and weakness of the urinary and rectal sphincters appeared. At times a girdle sensation was noticed and an ulnar parathesia became exceedingly troublesome. Her gait was distinctly ataxic and the Romberg symptom was two plus. The pupils were somewhat miotic, equal, regular in outline and were of the Argyll-Robertson type. The knee and ankle jerks were absent. The blood gave a negative Wassermann and lumbar puncture was refused. Under antisymphilitic treatment a decided abatement of the subjective symptoms was obtained.

THE OCULOCARDIAC REFLEX IN SYPHILIS OF THE CENTRAL NERVOUS SYSTEM.—E. Murray Auer, Indianapolis. *The Journal of the Medical Association*, 1917, vol. lxviii, p. 901.

Abolition of the oculocardiac reflex is among the earliest signs of syphilitic disease of the central nervous system and one of easy diagnosis practicability to the general practitioner. The oculocardiac reflex was abolished on the side exhibiting the hemianalgesia with preserved tactile sensation in the case presenting the Millard-Gubler syndrome. In only one case of well marked tabes with certain involvement in which pressure on the eyeball and



testes was not painful was there evidence of diminished or disturbed superficial sensation other than in the case mentioned above. In fifty-two per cent of the cases studied, the pulse rate ranged from 82 to 112, and the increased rate occurred chiefly among the well marked paretics. In the third nerve palsy, the ptosis can sometimes be overcome by the patient reinforcing the ptotic lid by forcibly holding the lids of the sound eye closed. During the paroxysms of spasmodic weeping occurring in pseudobulbar palsy, the radial pulse is practically imperceptible at the wrist, showing a reflex inhibition of the heart beat.

TWO CASES OF LATE CONGENITAL LUES.—Harry Apfel, New York. *New York Medical Journal*, 1917, vol. cv, p. 1032.

One of these cases presented quite an obscure condition when it first came under observation, and, while the other did show quite recognizable evidence of lues, still it raised doubts as to the proper diagnosis by the prompt disappearance of the objective signs without any internal treatment. It still further complicated the diagnosis by giving a negative Wassermann both in the patient's and in the mother's blood. The history in each case was of no material help, as is the case with a good many cases of hereditary syphilis. It is also of interest to note the type of bone lesion Case II presented. Usually the bone lesion is of a chronic nature with very little pain, affecting the bones of the leg, the phalanges, and occasionally the bones of the forearm. In this case the periostitis affected the humerus more or less acutely with considerable pain and tenderness, even giving the patient a rise of temperature. The interesting feature about the first case is the prompt disappearance of the syphilitic papules at the anal margin without any specific treatment.

CLINICO-ANATOMICAL INVESTIGATION OF A RAPIDLY FATAL CASE OF GENERAL PARALYSIS DUE TO ACQUIRED SYPHILIS.—T. E. Knowles, Edinburgh, and F. W. Mott, London. *The Lancet*, London, vol. xcii, p. 335.

The points which occur as being worthy of especial notice are:

1. The extreme rapidity which characterized the progress of the disease, six months and a few days only elapsing between the earliest observed symptoms and death.

2. The naked-eye signs of the disease were not apparent, and, but for the presence of the Wassermann reaction of the cerebrospinal fluid (during life and postmortem) and the finding of the spirochetes in the brain, it would have been difficult to have come to a decision as to the cause of the mental symptoms manifested during life.

3. The case is of interest in showing the value of the examination of the cerebrospinal fluid as a means of diagnosis in even the earliest stages of the disease; it is also of interest in the fact that the spirochetes were found in an emulsion of the apparently normal brain by the dark-field illumination method after five minutes' search.

4. The histological microscopic changes may be correlated with the characteristic clinical symptoms presented by the case for the comparatively short time prior to the fatal issue. It has been the experience of Mott to find that the spirochetes are more easily found in these rapidly fatal acute cases, in which microscopic changes are not evident, or not markedly so.

5. Contrary to the original statement of Noguchi, the spirochetes are found in the inflammatory cell infiltration of lymphocytes and plasma cells of the perivascular sheaths, rather than in the cortical brain substance; and that this has been my experience in other cases.

HERPES ZOSTER IN TABES DORSALIS AND GENERAL PARALYSIS OF THE INSANE.—Samuel L. Immerman, Philadelphia. *The Journal of the American Medical Association*, 1917, vol. lxxviii, p. 1609.

Of three patients having an attack of herpes zoster, two were paretics and one a tabetic. The cases of herpes zoster were of the symptomatic variety, that is, due to involvement of the ganglions in the pathologic processes of the disease from which the patients were suffering. The nature of the ganglionic changes is in all probability specific, that is, due to spirochetes or toxins.

A SKETCH OF MY RESEARCH ON SYPHILIS.—J. E. R. McDonagh, London. *The Journal of Cutaneous Diseases*, 1917, vol. xxxv, p. 230.

The *spirocheta pallida* is not the sole cause of syphilis, but only the adult male phase of the occidial protozoon-leucocytozoon syphilidis. Staining, although influenced in part by reaction, is also largely influenced by oxidation and reduction. Oxidation and reduction are either regulated by special ferments, or more probably by the hydroxyl and hydrogenions, which behave differently according to the "substratum" or physico-chemical nature of the bodies to which they are attached. Syphilitic serum is peculiar, in that the protein particles are more numerous and larger than they are in other diseases. The Wassermann reaction is a purely physical reaction, depending upon the number and size of the particles in the serum being tested. A positive Wassermann reaction means no more than the patient has presumably

had syphilis; it does not signify that the patient is actively syphilitic or that he necessarily requires treatment. The Gel test will give more information about a given serum than can be obtained with the Wassermann reaction. Chemotherapeutic agents are more organotropic than parasitotropic and act by altering the physical state of the protein colloidal particles in the serum. Metals act as oxidizing agents and nonmetals as reducing agents. As oxidation and reduction are regulated in corpora by iron and sulphur, better and safer therapeutic results can be obtained by using compounds containing these two elements than by using compounds containing such toxic elements as arsenic, antimony and silver.

THE SELECTIVE ACTION OF SPIROCHETES.—Morris Grossman, New York. *The Journal of the American Medical Association*, 1917, vol. lxxviii, p. 965.

Ophthalmoplegia interna is a rare condition; it may be familial. It may be the only objective evidence of congenital syphilis of the central nervous system. All offspring should be carefully examined for latent syphilis when the parents are known to be infected. When evidence of latent syphilis is found, treatment should be instituted; it must be continued until all clinical and biologic evidence of the disease disappears. In the cases cited the condition is due to a strain of spirochete which probably possesses a selective property for nerve tissue.

THE MERCURIC CHLORIDE TEST FOR THE DIAGNOSIS OF SYPHILITIC INFECTION.—E. G. Birge, Jacksonville, Fla., and J. Robbins Bean, Birmingham, Ala. *New York Medical Journal*, 1917, vol. cl, No. 21, p. 986.

The test as devised by Gordon is erratic. The precipitate varied in different serums; this apparently depends on some different chemical composition and is not affected by the presence or absence of syphilitic infection. The mercuric chloride test for the diagnosis of syphilitic infection should not be used.

THE WASSERMANN REACTION AS CARRIED OUT BY THE DEPARTMENT OF HEALTH.—John Koopman, New York. *Monthly Bulletin of the Department of Health, City of New York*, vol. vii, p. 42.

In view of the fact that all reagents used in Wassermann laboratories are derived in some manner from the blood or from the tissues of certain animals, and that they are all subject to more or less rapid deterioration, it is not surprising that the results sent out by the various laboratories sometimes vary; however, the var-

iation should never be so great as to produce contradictory findings. The antibody content of the patient's serum changes in some instances, in rather short periods. This has been repeatedly demonstrated by testing, at one time, two or more sera drawn on different days from the same patient. Every control and check is carried out both in the technical and in the clerical work, incident to recording and reporting results. Physicians can do a great deal in helping the Department maintain a prompt and efficient service, if they will take as much care in forwarding specimens as they expect the laboratory to take with the examinations. To what extent physicians are responsible for unsatisfactory reports is shown by the fact that in 1916 a total of 3,000 specimens were received which could not be examined; some were received in too poor condition to be tested, or had leaked out before reaching the laboratory. Others were sent in with histories to which the physicians had failed to sign their names. The Department of Health appreciates any opportunity to improve the service of the laboratory and will cheerfully investigate any complaint as to the accuracy of the reaction.

LANGE'S COLLOIDAL GOLD TEST.—J. H. Black, Dallas, Tex. *Texas State Journal of Medicine*, 1917, vol. xii, No. 11, p. 435.

The colloidal gold test of the spinal fluid is of much value in the diagnosis of diseases of luetic origin in the central nervous system. Good colloidal solutions require for their preparation good glass, pure water and chemicals, accurate measurements, and careful manipulations. A simple equipment and technic is described which provided uniformly good solutions.

THE DIAGNOSTIC AND PROGNOSTIC SIGNIFICANCE OF SPINAL FLUID FINDINGS IN SYPHILIS.—John A. Fordyce, New York. *Medical Record*, 1917, vol. xci, p. 930.

Tabes, paresis and certain types of cerebrospinal syphilis originate in fluid infection in the secondary stage. Our hope in preventing degenerative changes with permanent mental or physical disability lies in the systematic examination of the spinal fluid before the patient is discharged as cured. The fluid may contain spirochetes with few or no symptoms until an acute condition is precipitated such as aphasia or localized paralyses. We may summarize the prognostic significance of spinal fluid findings somewhat as follows: A complete arrest of the pathological changes may be anticipated in early syphilis by intensive treatment. This applies to the presence of a paretic curve with the other phases positive. In tabes with a pleocytosis, a positive Wassermann in the low dilutions and luetic curve the prognosis is favor-

able, as to arrest of the meningitis and prevention of the extension of the degeneration. We have a number of cases with persistent negative findings with absence of symptoms. In cerebrospinal syphilis response to treatment is usually prompt and the results permanent in the absence of secondary areas of softening, as hemorrhage following endarteritis.

THE ADVISABILITY OF A MORE GENERAL USE OF THE WASSERMANN TEST IN THE SERVICE.—G. F. Clark, Passed Assistant Surgeon, United States Navy. United States Naval Medical Bulletin, 1917, vol. xi, p. 179.

The following recommendations are made:

(1) Wassermann tests for all patients admitted to a United States naval hospital.

(2) Wassermann tests for all recruits before they are sent into general service; for every man who reenlists; for all candidates for original appointment as commissioned officers.

(3) A period of observation with Wassermann tests for every man having a genital sore, no matter how insignificant.

ON THE RELIABILITY OF THE WASSERMANN REACTION.—Reuben Ottenberg, New York. The Archives of Internal Medicine, 1917, vol. xix, p. 492.

Divergent reports on identical serums sent to different laboratories undoubtedly occur and will continue to occur so long as laboratory workers continue to use widely different technical methods. These divergent results, however, should not shake our confidence in the clinical specificity of the Wassermann reaction. They almost invariably occur in cases which exhibit weakly positive reactions, and they usually mean that one laboratory has succeeded in detecting a weakly positive reaction, while the other has not. In the great majority of cases which present definite positive or definite negative results, the reports of different laboratories are practically uniform. The reason for the divergence in results on weakly positive cases is that some laboratories have adopted certain refinements of technic which other laboratories have for various reasons failed to adopt. The original Wassermann technic, while safe in the sense of not giving false positive results, is not nearly so delicate in detecting weakly positive tests as it can be made. Many of the devices for making the reaction more delicate without impairing its safety are discussed and recommended in the present paper. On the other hand there are a few workers who, in their anxiety to detect as many of the weakly positive cases as possible, have adopted methods which easily can

and probably do lead to occasional false positive reports. Though the technic of the Wassermann reaction is relatively simple to learn, the work is full of pitfalls and should be done only by properly trained workers and the results should be controlled by every possible control. While it does not seem possible that all workers will adopt one uniform technic, it is greatly to be desired that they should agree on basic principles and methods. Though the present paper has discussed the Wassermann reaction only, the observations are nearly all applicable (with due control of specificity) to complement fixation with bacterial and other specific antigens.

THE PROVOCATION OF THE LUTIN TEST IN NONSYPHILITIC PATIENTS.

—H. M. Cole and H. V. Paryzek, Cleveland. *The Journal of the American Medical Association*, 1917, vol. lxxviii, p. 1091.

Out of thirty-nine cases tested by the luetin reaction, two normal persons gave pustular reactions to the control test. Among eighteen taking potassium iodide, sixteen gave positive reactions, these being mostly strongly positive in those patients who had received from 200 to 600 grains. This action is found not to be specific for potassium iodide alone, as it was caused, though in a lesser degree, by sodium bromid in three cases tested, by potassium nitrate in six out of eight cases tested, and by calcium bromid and by sodium iodide each in one case tested.

A COMPLEMENT FIXATION TEST FOR SYPHILIS USING HUMAN COMPLEMENT.—Sara B. Myer, Chief Nurse, United States Navy. *United States Naval Medical Bulletin*, 1917, vol. xl, p. 175.

The following test has been developed in hope that it may prove generally useful by reason of the simplicity of the technic, the elimination of animals for complement and red blood cells, and the ease of interpretation. The reagents can be easily obtained and preserved. In using the test in a long series of cases, nothing has developed to discredit the value of human complement, and, indeed, it has been observed that the anticomplementary action of different human sera is less marked when using human complement than when using guinea-pig complement, thereby requiring a smaller margin for anticomplementary absorption, and allowing the test to be made more delicate. It has been found that the absolute unit of amboceptor—"the least amount that will give complete hemolysis under any circumstances"—may be ascertained with greater precision when using human complement than when using guinea-pig complement. Each patient's blood is drawn from a vein with a 2-mil syringe and medium sized needle, and put into a centrifuge tube with his name and number. After standing

15 minutes, the blood is centrifuged to separate the serum, and inactivated by heating at 56° C. for 20 minutes in an incubator. A known negative and a known strongly positive serum are always included in the series. Tubes for the test are 6 mm. (inside diameter) by 6 cm., and are set up in racks in pairs, each pair being numbered, one pair for each patient. The front row contains antigen and is the test, while the back row is the control without antigen. A capillary pipette is graduated to 0.05, 0.1, 0.25 and 1 mil. The amounts used in the tests are as follows:

	Mil
Antigen dilution .....	0.25
Complement dilution .....	.05
Patient's serum .....	.10
Sensitized red cells (composed of amboceptor solution)..	0.05
5 per cent red cell suspension.....	.05
Total volume .....	.50

The salt solution used is 0.9 per cent aqueous sodium chlorid. The technic for the test is very simple. Having made up the red cell suspension and the amboceptor paper solution, titrate the complement as directed below, and choose the dilution to be used in the test. Now proceed with the actual test. Mix equal parts of the amboceptor solution and the red cell suspension and place in the incubator to sensitize for 30 minutes, shaking frequently, as the cells tend to agglutinate. Now set up a pair of tubes for each serum to be tested with 0.1 mil of serum in each tube, washing pipette thoroughly after each pair. Add 0.05 mil of the chosen dilution of complement to each tube, and 0.25 mil of salt solution to each tube in the back row, and 0.25 mil of antigen dilution to each in the front row. Shake well and incubate for 25 minutes. Then add 0.1 mil of the sensitized red cell suspension to each tube, shake, incubate for 15 minutes, shake again, and allow to settle for 30 minutes. Read in usual manner. The red cell suspension is prepared in the following manner. Two graduated centrifuge tubes are filled to 10 mils with 1 per cent sodium citrate in salt solution. (Two tubes are prepared as one may be broken.) As each patient's blood is drawn, a few drops are added to the solution in the tubes—about 1.5 mils in all. The red cells are thrown down in the centrifuge, washed five times with salt solution, and then made up to 5 per cent in same. The red cells are sensitized for the test and also for the titrations by mixing equal parts of this suspension with the amboceptor solution, and incubated at 37° C. for exactly 30 minutes. The amboceptor solution is prepared by extracting 5 Noguchi units of antihuman amboceptor paper in 1 mil of salt solution at room temperature for exactly 30 minutes and then filtering.

Enough of this solution must be prepared to allow 0.05 mil for each tube in the series and titrations, and at least 1.5 mils for waste. The filter paper takes up about 1 mil. To titrate, different amounts of this solution are mixed with 0.05 mil of 5 per cent red cell suspension, each tube being made up to 0.45 mil with salt solution, and incubated for 30 minutes to sensitize. The titration is completed by adding 0.05 mil 100 per cent human complement (fresh serum) to each tube, and incubating for 15 minutes. It has been found that 0.05 mil is usually equivalent to 1.5 units. This unit is practically constant, and this titration need not be done before each series. The complement is titrated before each series. To do this, six tubes are set up, each containing 0.35 mil salt solution, 0.05 mil amboceptor solution (1.5 units), and 0.05 mil 5 per cent red cell suspension. These are then incubated for 30 minutes to sensitize, shaking three times during the incubation. While waiting for this, six dilutions of human complement from known negative cases (mixed sera if possible) are made up in small amounts—75 per cent, 66⅔ per cent, 50 per cent, 40 per cent, 33⅓ per cent, 25 per cent. When sensitized, each of the above tubes has added to it 0.05 mil of one of these dilutions. They are then shaken, and incubated for 15 minutes. The tube containing the least amount of complement which shows complete hemolysis is noted, and this amount of complement plus 15 per cent is the amount used in the test. For instance, if 50 per cent gives complete hemolysis, then 66⅔ per cent is used in the test. The acetone-insoluble antigen obtained from the United States Naval Medical School is titrated with this hemolytic system, and used in a strength equal to one-fifth of its least anticomplementary dose—usually 0.25 mil of a 1 to 100 dilution—providing this is equal to at least 5 antigenic units as titrated with a strongly positive serum.

A "LUETIN" REACTION IN SYPHILIS PRODUCED BY AGAR.—John H. Stokes, Rochester, Minn. *The Journal of the American Medical Association*, 1917, vol. lxviii, p. 1094.

Agar hydrosol, from 0.5 to 0.7 per cent in physiologic sodium chlorid solution, when injected intradermally in doses of 0.1 c.c. gives reaction clinically similar to those produced by luetin. Controls of equal amounts of sterile olive oil, producing similar trauma, do not give rise to reactions. The agar reaction differs from the luetin reaction chiefly in a tendency to a more torpid course and a slower development. Papular and pustular reactions may be produced, the latter being somewhat more hemorrhagic than those produced by luetin. The percentage of positives in known syphilis, eliminating doubtful reactions, varied in two series aggregating forty cases, from 50 to 70 per cent. The normal persons and



nonsyphilitics in my series did not react. The only positive case in which syphilis seemed to be eliminated was a case of urticaria pigmentosa with factitial urticarial phenomena. Two patients with gonorrhea in a total series of seventy-six reacted positively. Both were receiving vaccines with marked reactions. One patient with syeosis barbae receiving vaccines with marked reaction, also reacted positively to the agar. The influence of iodids could be eliminated from the series in which 50 per cent reacted positively. The positive reaction to agar as brought about by the internal administration of iodids, was observed in typical form in three cases. It is simply a severe form of the luetin and agar reactions. In two cases in which iodids were being administered, the reaction to agar was negative. The cutaneous reaction to both luetin and agar in syphilis is interpreted as nonspecific in character and as a colloidal absorption phenomenon in a hypersensitive or labile skin.

A STUDY OF TWO HUNDRED AND NINETY POSTMORTEM WASSERMANN REACTIONS.—Stuart Graves, Louisville, Ky. *Mississippi Valley Medical Journal*, 1917, vol. xxiv, p. 118.

Postmortem Wassermann reactions confirmed antemortem reactions in 95 per cent of 38 control cases. Positives were confirmed in serum six hours postmortem and negatives in serum twenty-four hours postmortem. In 90.4 per cent of cases showing postmortem anatomic lesions of syphilis, or presenting positive evidence of syphilis in their histories, the sera postmortem gave positive Wassermann reactions. The fact that positive postmortem reactions appeared in 38 cases, which did not present postmortem lesions or historic evidence of syphilis and in which death was due to acute infections, tuberculosis or malignant tumors, can not be interpreted to mean that the reaction was caused by those diseases, because in the first place, the histories and autopsies in those cases were not nearly enough complete to rule out syphilis, and in the second place, because sera from 94 patients who died of acute infections, tuberculosis or malignant tumors, examined under similar conditions, gave negative reactions. Only 7 per cent of 282 cases showed negative reactions in the presence of anatomical lesions (aneurysms) characteristic of syphilis. The reactions conformed to the anatomic and historic evidence in 84 per cent of the cases. The fact that only eight, or 3 per cent of the sera were anticomplementary indicates that the sera were in good condition. The average percentage of specific reactions was almost as high postmortem as would be expected antemortem. The positive reaction appeared in twice as many males as females, in three times as many negroes as whites and in white females in only 4.3 per cent of the cases examined. The Wassermann reactions, performed on postmortem

blood according to methods followed in this investigation, is a reliable aid to the diagnosis of syphilis.

**PUNCTURE HEADACHE.**—Charles L. Dana, New York. *The Journal of the American Medical Association*, 1917, vol. lxviii, p. 1017.

The headache rarely begins until the day following the puncture, when the patient usually is allowed to get up. It may start, however, directly after operation or come on three days later, depending on the activities of the patient and the conditions of the cerebrospinal fluid circulation. The condition lasts with remission for from five or six days to two or three weeks. When the trouble lasts and is obstinate, there is an accompanying cerebral dysphasia and sense of confusion or giddiness. The symptom is more common in patients whose cerebrospinal fluid is negative, and in whom the fluid comes out under low pressure. In other words, the healthy cord reacts badly to puncture. The headache can usually be prevented by keeping the patient in a horizontal position for three or more days. After the headache occurs, the effective measure is to return the patient to bed. Possibly the very slow removal of the fluid in minimal amounts (2 c.c.) may be effective. Abdominal compresses may also help.

**THE FOUR PLUS WASSERMANN.**—D. M. Kaplan, New York. *New York Medical Journal*, vol. cv, p. 728.

One must regard with suspicion a positive result in patients with a hepatic disturbance as some liver diseases where lues can be excluded show a positive reaction in the serum. To give only brief mention of the conditions that at times give a plus Wassermann with lues satisfactorily excluded: We have certain forms of lepra, certain malaria, scleroderma, certain forms of scarlet fever, and of late the study of internal secretions tend to show that certain endocrine types may give a positive result without giving in the anamnesis a hint of lues (Pseudo-Tabes Pituitaria, Oppenheim.) Such patients do not improve under the specific treatments and must be studied on endocrine lines. Carcinoma may give a positive reaction, particularly when the hepatic apparatus is involved. Achylia gastrica without lues may give rise to a nonspecific plus. Diabetes with acidosis gives at times a plus result. We need not go into the many tropical diseases that furnish a nonspecific result; the conditions enumerated and many others still to be observed compel attention and require great care and greater sacrifice on the part of the doctor who sees in the report a possible nonspecific Wassermann.

MODE OF ABSORPTION OF MERCURY IN THE INUNCTION TREATMENT OF SYPHILIS.—Udo J. Wile and Joseph A. Elliott, Ann Arbor, Mich. *The Journal of the American Medical Association*, 1917, vol. lxvii, p. 1027.

The mode of absorption of mercury in the inunction cure is both by volatilization and by direct absorption through the skin. Non-volatile salts of mercury are absorbed through the skin, but their elimination and their absorption are far slower than in the absorption of those salts having a high vapor pressure. The more rapid appearance of mercury in the urine in the case of the volatile salts is probably due to the combined action of the volatilization and inhalation through the lungs and absorption through the skin. In the order of rapidity of absorption, mercurial ointment ranks over calomel, although the latter is appreciably absorbed through volatilization. As the therapeutic effect of mercury is probably in proportion to the rapidity and degree of absorption, there can be no question that the volatile salts should not be superseded in the inunction cure by the nonvolatile salts, even though the latter have the advantage of cleanliness. As calomel is obviously a cleaner preparation, and further, as it is absorbed both by volatilization and directly through the skin, further study should be undertaken to determine whether its therapeutic effect may not justify its substitution for mercurial ointment.

DIAGNOSIS OF SYPHILIS OF THE NERVOUS SYSTEM.—Edward Livingston Hunt, New York. *Medical Record*, 1917, vol. xci, p. 581.

To make a thorough and reliable diagnosis in syphilis of the nervous system necessitates six things: (1) A knowledge of certain facts, (2) a clinical examination, (3) a blood examination, (4) a lumbar puncture, (5) an x-ray picture, and (6) common sense. A few of the facts that should be known are that syphilis of the nervous system occurs much oftener than is suspected; that in syphilis of the brain no typical picture is evident, and that tabes and paresis are now recognized as the direct results of syphilis. In the clinical examination there are no very new developments. Great care must be exercised upon the part of the clinician, and great emphasis placed upon the evidence obtained from the examination of the heart and circulation. In syphilis of the nervous system an aortic insufficiency, a dilated aorta, and high blood pressure are almost as common as sluggish pupils and abnormal reflexes. In tabes, Swift teaches that squeezing of the Achilles tendon will produce great pain, and in the same disease it has been known that absence of the Achilles jerk precedes the loss of the knee jerk. In the blood examination, the one factor is the Wassermann test. It is, however, neither the only nor the final arbiter. A few points to remember are: That a negative Wassermann re-

action in the blood often accompanies a positive Wassermann reaction in the spinal fluid; that the Wassermann is a quantitative test and should be reported in its various dilutions; that laboratories vary, due to the difference in technic employed; that the ingestion of considerable quantities of alcohol by the patient within twenty-four hours of taking his blood may change a positive into a negative reaction; and finally, that the Wassermann reaction itself varies widely from day to day. The practitioner who deems the lumbar puncture superfluous, or too painful, is wrong. He is falling behind, and, instead of saving, he is injuring his patient. The colloidal gold test should be required in every laboratory test. It is daily increasing in value and importance. The x-ray pictures the chest; it is more reliable and more accurate than percussion in both diagnosis and prognosis. It should never be omitted and will often reveal a hitherto unthought of aneurysm or aortitis. Common sense is the last of the six factors which is deemed necessary in making a thorough and reliable diagnosis in syphilis of the nervous system.

THE MODERN DIAGNOSIS AND TREATMENT OF SYPHILIS.—B. A. Thomas, Philadelphia, and Chas. H. J. Barnett, Philadelphia. New York Medical Journal, 1917, vol. cv, p. 883.

The treatment of syphilis, notwithstanding the promise of salvarsan and its substitutes, judged from the excellent serological results, extending in many instances over several years, remains, in a sense, empirical. The ultimate proof of cure does not rest necessarily upon continuously negative Wassermann reactions for one, two, three, five, ten, twenty, or even forty years, but rather upon complete freedom from symptoms for a generation or more. The Wassermann reaction furnishes the best control of treatment and is the most reliable index of cure subsequent to proper treatment. The sheet anchor in the treatment of syphilis is no longer mercury, but salvarsan, neosalvarsan, or one of their substitutes. It is of paramount importance however, that the injections of arsenobenzol in the beginning be administered as early as possible and intensively in full doses commensurate with the physiological tolerance of the patient, not scattered indefinitely over months, interspersed here and there with a Wassermann test. In view of the possibility of immediate cure by this drug properly administered in the primary if not the secondary and latent stages of the disease, the treatment of syphilis, particularly in the chancre period, prior to the advent of a positive Wassermann, becomes an emergency operation, in many instances no less imperative than the administration of antitoxin in diphtheria. Our experience dictates, as a reliable routine, two injections of salvarsan in the early chancre stage; at least three injections in the late primary and throughout

the secondary or latent stage of the disease, and during the tertiary and hereditary forms of syphilis not fewer than four to six injections, supplemented by mercury and the iodides. If, after such treatment, the Wassermann still appears positive, a second series of injections should be administered. Serologically judged on a three month to a five year duration, syphilis, in the chancre stage, if diagnosed early, either clinically or if necessary by either the dark-field microscope or the Wassermann reaction, may be cured by two injections of salvarsan or neosalvarsan; indeed, if the diagnosis is made, particularly before the advent of a positive Wassermann, one dose of either of these drugs may be sufficient. Secondary syphilis seems to do just as well without as with mercury, providing enough salvarsan or neosalvarsan is given to produce a negative Wassermann. The serological result in tertiary syphilis treated intensively with salvarsan and its substitutes are not so brilliant as those of the secondary period. The French preparation of arsenobenzol and the Canadian diarsenol are excellent products and may be just as efficient as salvarsan and neosalvarsan, but on account of their greater tendency to toxic phenomena are not destined to supercede the original German products. Likewise arsenobenzol, owing to its lesser potency in the reduction of the Wassermann reaction, must be regarded as inferior to the German products. The arylarsonate "soamin" and sodium caeodylate, both clinically and serologically, have no place in the effective treatment of syphilis. Sociologically, in view of the fact that less than twelve per cent of our hospital syphilitics return for treatment until discharged cured, a problem is presented which urgently demands the co-operation of our civil authorities and health boards for the necessary control and treatment of this disease, not, however, to be realized until all hospitals receiving state aid are compelled to maintain evening dispensaries with paid attendants for the proper treatment and admission, when necessary, of venereal patients.

**TOXIC EFFECTS FROM NEOSALVARISAN.**—Cland G. Hoffman, Louisville, Ky. *The Urologic and Cutaneous Review*, 1917, vol. xxi, p. 255.

The author describes a case of a male of 36 years who was given by mistake 0.6 gm. of salvarsan, mixed with 10 c.c. freshly distilled water; only a portion of the drug was dissolved; nearly all of the solution was neutralized and about one-half of the fluid was injected in the right cephalic vein. Almost immediately the patient complained of a choking sensation and became extremely pale with weak pulse and labored respiration. Urinary suppression ensued and on the second day the patient complained of weakness, chilliness and general muscular discomfort. Phlebitis occurred in the

injected vein and extended to the shoulder; the arm was red, swollen and painful. This manifestation subsequently increased in severity and the temperature reached 102.4°. Urinary secretion was finally reestablished in about six weeks. In several instances during the past year the author has seen violent systemic reactions or toxic effects following the intravenous administrations of neosalvarsan, the preparation of the solution and manner of injection being identical with methods formerly employed when no such manifestations occurred. He has seen only one case in which the reaction appeared twenty-four hours after intravenous injections of neosalvarsan or salvarsan, and is convinced that this toxic manifestation was due to variation in the quality of the preparation which has been used during the past year.

RECENT ADVANCES IN THE TREATMENT OF SYPHILIS.—E. E. Waters, London. *The Indian Medical Gazette*, 1917, p. 24.

Early diagnosis and early treatment are of the greatest importance. Once the diagnosis is made, salvarsan or galyl should be given intravenously, followed by mercurial injections. Freshly distilled water should be used and the patient properly prepared. Caution must be exercised in giving salvarsan or galyl to cases in bad health, particularly when the kidneys or skin are affected. Galyl may be given safely in pregnancy. Repeated courses of galyl and mercury may be required to effect a cure, and in all cases where the nervous system is affected, the cerebrospinal fluid should be examined and, if necessary, salvarsanized (or "galyzied") serum should be injected intrathecally, and iodides given freely.

INTRASPINOUS INJECTIONS OF NEOSALVARSANIZED SERUM IN NERVOUS AND MENTAL DISEASES.—Alfred Gordon, Philadelphia. *New York Medical Journal*, 1917, vol. cv, p. 876.

The results obtained in the 212 cases are bound to create a spirit of optimism in the management of cases with evidence of syphilis. In some cases the expectation is greater than in others, as for example in early cases. In some cases the amelioration of the nervous and mental manifestations are short of being considered brilliant and indeed it is apt to render one highly enthusiastic. But a calmer consideration of the actual facts, especially when the cases are followed up for a sufficiently long time, does not permit the author to be over-sanguine in spite of the favorable results obtained in the majority of cases. There were sufficient recurrences to warrant a conclusion that the last word in the treatment of nervous and mental diseases of syphilitic origin is far from having been spoken. On the other hand, a mere comparison of the results obtained from the old methods of treatment with those

from the newer procedures must convince an impartial observer that the latter are much superior to the former. The largest number of the author's cases, except the psychoses, had been treated with mercurials and iodides for a considerable time prior to coming under the author's observation with slight or no traces at all. The cases in which some success had been obtained with those remedies can not stand comparison with the cases to which the intraspinal treatment has been applied. In the latter the results have been at times so strikingly satisfactory that for the present at least it appears to be the only procedure in which hope can be placed for checking syphilitic diseases of the nervous system. A procedure that enables us to bring spirocheticidal reagents into direct contact with the cerebrospinal system, intraspinally and intra-cerebrally, seems to be the most logical one. The fact itself of giving satisfactory results in most serious affections is most encouraging and promising. It points the way in which our efforts should be directed. The future success lies in the perfection of this method.

**SYPHILIS OF THE NERVOUS SYSTEM.**—Chas. L. Gregory, Greenville, Tex. *The Journal of the Arkansas Medical Society*, 1917, vol. xiii, p. 253.

Syphilis of the nervous system is only syphilis, and not a nervous disease. We can and should recognize syphilis of the nervous system by proper examination in its early stages. Syphilis of the nervous system responds to treatment in its early stages to any and all measures which cure syphilis. In its later stages, after death to the nerve cells, it is incurable by any measure.

**NOTE ON A CASE WITH SEVERE GASTRIC CRISES TREATED BY AACHEN METHODS.**—Reginald Hayes, England. *The Lancet*, London, 1917, vol. xcii, p. 652.

In all cases of syphilis of the nervous system it is eminently advisable that prolonged inunction should be tried. It is best tolerated when given with the sulphur water, internally and externally, as at Aachen. If scrupulous attention be paid in detail in the administration, no ill effects can follow, and it is as a rule well borne. The method in every particular has now for some years been carried out in this country, where the patient has the added advantage of keeping in close touch with his usual medical attendant. This patient paid thirteen visits to Aachen and underwent 698 rubbings. It was not until 108 inunctions had been given that definite improvement was noted and the crises ceased. He was never salivated, nor did he suffer from gingivitis. His weight is now normal for his height, and has increased 3 st. since the beginning of the treatment. His capacity for work and play is now considerable.

## ORGANIZATION OF THE AMERICAN ASSOCIATION FOR THE CONTROL OF SYPHILIS

THERE was organized at Cincinnati on May 23rd and 24th, the "American Association for the Control of Syphilis," the objects of the Association to be the promulgation of knowledge of syphilis among medical men, medical institutions, boards of health, hospital boards, dispensary attendants and boards, and other organizations having the care and treatment of syphilis.

Those composing the charter membership hope to develop the important social and economic sides of this disease. Plans are also being made to collect standardized statistics from the various institutions now treating syphilis; to further the establishment of free clinics and dispensaries for the diagnosis and treatment of syphilis; and to encourage the more comprehensive teaching of syphilis in medical schools.

The Association will operate through a national body and local branches in various cities, probably in close cooperation with the American Social Hygiene Association, the former to interest themselves in the purely medical side of the work which is not entirely covered by the latter Association.

The membership of the Association at present is composed of the following:

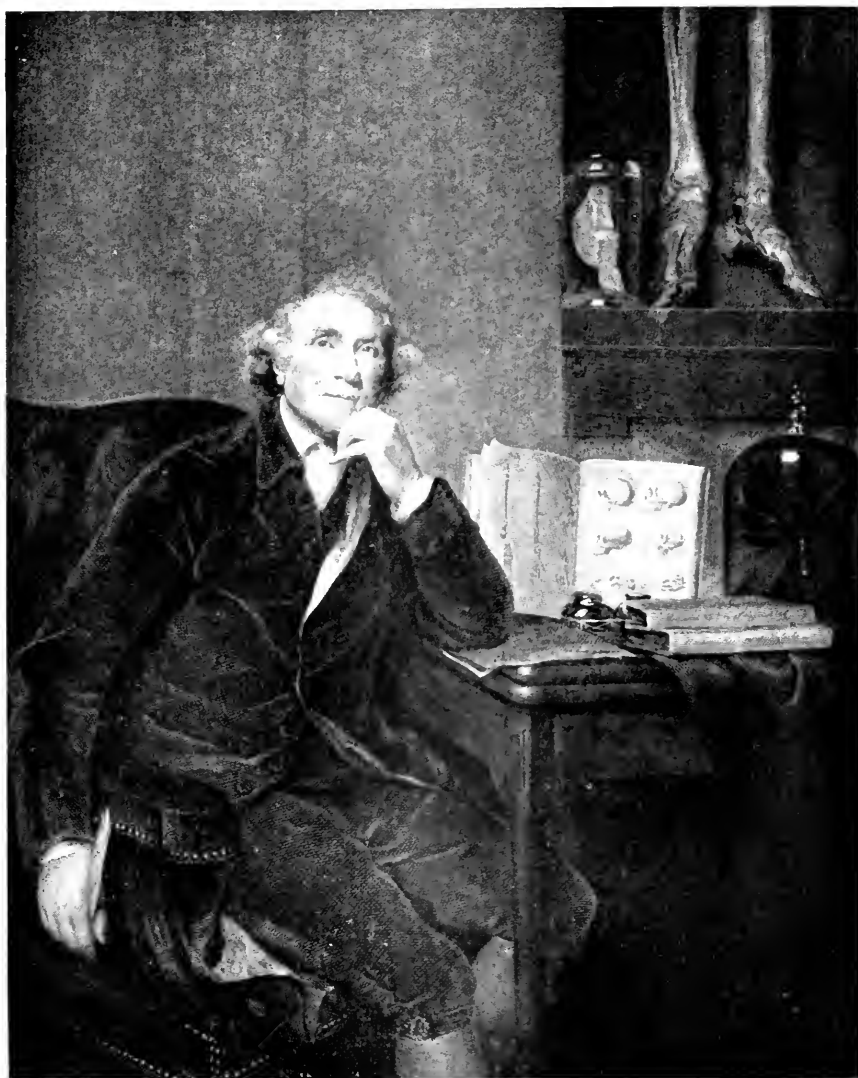
Dr. W. T. Belfield of Chicago,	Dr. Oliver Ormsby of Chicago,
Dr. Ernest D. Chipman, of San Francisco,	Dr. Sigmond Pollitzer of New York,
Dr. W. T. Corlett of Cleveland,	Dr. W. A. Pusey of Chicago,
Dr. Isadore Dyer of New Orleans,	Dr. A. Ravogli of Cincinnati,
Dr. M. F. Engman of St. Louis,	Maj. Matthew Reasoner of Washington,
Dr. J. A. Fordyce of New York,	Dr. J. F. Schamberg of Philadelphia,
Dr. Marcus Haase of Memphis,	Dr. Morton Smith of Boston,
Dr. H. H. Hazen of Washington,	Dr. W. F. Snow of New York,
Dr. M. B. Hartzell of Philadelphia,	Dr. H. W. Stelwagon of Philadelphia,
Dr. H. F. Kleinschmidt of St. Louis,	Dr. G. H. Walker of Baltimore,
Dr. G. M. MacKee of New York,	Dr. Grover Wende of Buffalo,
Dr. E. L. McEwen of Chicago,	Dr. Udo Wile of Buffalo,
Dr. W. H. Mook of St. Louis,	Dr. J. M. Winfield of Brooklyn,
Dr. H. Morrow of San Francisco,	Dr. H. R. Varney of Detroit.
Dr. H. J. Nichols of San Francisco,	

The following officers were elected: Dr. M. F. Engman, President; Dr. J. F. Schamberg, Vice-President; Executive Committee: Dr. J. A. Fordyce, New York; Dr. Sigmond Pollitzer, New York; Dr. W. A. Pusey, Chicago; Dr. Grover W. Wende, Buffalo; Dr. H. E. Kleinschmidt, Secy.-Treas., 607 Federal Reserve Bldg., St. Louis, Mo.





EPOCH-MAKING CONTRIBUTIONS  
TO THE STUDY OF SYPHILIS



JOHN HUNTER

(SEE PAGE 821)

# The American Journal of Syphilis

A QUARTERLY JOURNAL DEVOTED TO THE  
STUDY AND PREVENTION OF SYPHILIS

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## Original Articles

### SYPHILIS OF THE PULMONARY ARTERY: SYPHILITIC ANEURYSM OF LEFT UPPER DIVISION: DEMON- STRATION OF SPIROCHETE PALLIDA IN WALL OF ARTERY AND ANEURYSMAL SAC\*

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(Received for publication, September 29, 1917)

SYPHILIS of the pulmonary artery is considered one of the great rarities. There is but little literature concerning it. The ordinary textbook does not mention it. The few cases reported in which lesions of the pulmonary artery wall were regarded as syphilitic, rest entirely upon the character of the histologic changes. *Spirochete pallida* has not, up to the present time, been demonstrated in these lesions. It follows, therefore, that only those lesions of the pulmonary artery definitely *gummatous* in character can have been regarded as syphilitic with any degree of certainty. This criterion narrows greatly the number of observations in which the changes in the pulmonary artery can be accepted as in all probability syphi-

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\*Presented before the International Association of Medical Museums, New York, April 5, 1917.

litic. We may conclude from this that gummatous changes, at least, are of very rare occurrence in the pulmonary artery.

Nevertheless, sclerotic and atherosclerotic changes in the pulmonary artery have been so much more frequently mentioned in the literature that we must believe that lesions of this type must be of far greater frequency than gummatous lesions. The part that syphilis plays in the etiology of these sclerotic processes has, however, been very difficult of determination; and very few authors have ascribed to syphilis any important role in their production. By the great majority of observers the atherosclerosis of the pulmonary artery of the moderate degree so often seen at the autopsy table has been regarded as but an incident in the picture of a general atherosclerosis, or as resulting from long continued increase of blood pressure in the pulmonary vessels in such conditions as mitral stenosis, emphysema, etc. In these cases the pulmonary atherosclerosis is without clinical significance. In but a small number of cases (Mönckeberg, Romberg, Aust, Rogers, Sanders, Barlaro, etc.) has there been observed an extensive pulmonary atherosclerosis apparently of primary clinical importance (symptoms of chronic cyanosis, etc.). The writer has under study the autopsy material of such a case of pulmonary atherosclerosis presenting clinically the picture of polycythemia. These cases probably fall into the class styled "Ayerza's disease" by Barlaro.

Macroscopically these most common forms of pulmonary atherosclerosis consist usually of yellowish or yellowish-white, more rarely porcelain-like, thickenings of the arterial wall, chiefly of the intima. These thickenings are usually elevated, and may be plaque-like or nodular, or more diffuse. Calcification is rare; and atheromatous ulcers appear not to have been observed. (In my case of chronic polycythemia there were extensive atheromatous ulcers in the pulmonary arteries.) Microscopically the lesions have been described as similar to those of general atherosclerosis, consisting essentially of a thickening of the intima with hyaline change of the fibrous tissue and secondary atheromatous degeneration. The relation of syphilis to these changes in the pulmonary artery has been as much disputed relatively as it has been in the case of systemic atherosclerosis. At the present time the majority of writers regard them as nonsyphilitic in origin.

As to the occurrence in the pulmonary artery of the form of

mesarteritis that very recently has come to be pretty generally regarded as syphilitic in etiology (since it occurs in the aorta of all known syphilitics coming to autopsy, and has been shown to be associated with spirochete localization) but little is known. In the aorta this type of vessel lesion is characterized macroscopically by thickening, or often thinning, of the vessel wall, with loss of elasticity, hyaline change without much tendency to calcification or atheromatous change, and linear or radiating contractures or fissures of the intima. Microscopically the essential syphilitic characters of this process are the lymphocyte and plasma-cell infiltrations along the vasa vasorum of the adventitia and media, obliteration of these vessels, atrophy, fibrosis, hyaline change and secondary atheromatous changes in intima and media. In my experience mesaortitis of this type is always syphilitic. I believe, however, that healed syphilitic mesaortitis can not be distinguished microscopically from ordinary atherosclerosis; and, on the other hand, the macroscopic appearances of ordinary atherosclerosis may yield the microscopic picture of an active syphilitic process. I also believe that the terms "mesaortitis" and "mesarteritis" are misapplied. All coats of the vessel are involved; and the most active process is usually found in the adventitia. It is essentially a disease involving the vasa vasorum; and the changes in the intima and media are secondary to the disturbance of circulation in the small nutrient vessels of the artery. They consist of a slow atrophy, fibrosis, secondary hyaline change and atheromatous degeneration; and are perhaps to be interpreted as of the nature of a slow infarction. The essential diagnostic features of this form of syphilitic disease of the vessels are the active infiltrations about the vasa vasorum. The macroscopic picture may be characteristic (as described above) in some cases, but in many the gross changes may be wholly those of ordinary atherosclerosis. The microscopic appearances alone can decide the question; and this only when the process is still active. In these active perivascular (vasa vasorum) infiltrations the spirochete may be found in properly-prepared Levaditi blocks made from cadavers still warm.

The occurrence of this form of syphilitic arteritis leading ultimately to atherosclerosis has been noted almost wholly in the aorta; and the other large arteries of the body have not been given much attention with respect to their involvement in the process. As far as the pulmonary artery is concerned there exist a very few obser-

vations in which this type of arteritis was found affecting this vessel. These observations will be listed below.

The subject of aneurysm of the pulmonary artery also receives very scant attention in the textbooks and general literature. It is not mentioned at all by the majority of writers. Benda, *Aschoff's Spezielle Pathologie, Zweite Auflage*, 83, says that of the visceral arteries the cerebral, pulmonary and splenic arteries are most frequently the seat of aneurysms. He undoubtedly refers to the small aneurysms of the size of a pea or bean found in tuberculous cavities, and from which fatal hemorrhage frequently takes place. These are mentioned also in the articles on pulmonary tuberculosis. The writer has been unable to find in any textbook any mention of syphilitic aneurysm of the pulmonary artery. Of the reviews of the general literature on the subject of pulmonary aneurysm the monographs of Henschen (1906) and Posselt (1909) are the most important and complete.

#### SURVEY OF LITERATURE

The literature of syphilitic disease of the pulmonary artery has been reviewed by Posselt up to the year 1909. He calls attention to the fact that although a luetic basis for arteriosclerosis of the pulmonary artery was early suspected the majority of the cases reported rested upon very vague surmises. In others the syphilitic nature of the changes in the pulmonary artery was assumed because of a history of syphilis in the patient, or because luetic processes were found in other organs. The majority of the reported cases were observed before the discovery of the spirochete and the Wassermann reaction; and in a large number the pathologic description is too poor or too incomplete to permit definite conclusions as to the nature of the process.

Neumann, in his article on syphilis in the *Nothnagel System*, 1896, says: "An idiopathic syphilitic diffuse inflammation of the pulmonary artery has to my knowledge not yet been observed."

Posselt says that so far as he can see the arteriosclerotic processes in the pulmonary artery lack the specific characteristics that are present in endoaortitis luetica, although in a few cases the descriptions come close to it. He further says that luetic processes in the pulmonary artery must be extraordinarily rare since the great textbooks and handbooks of internal medicine, pathologic anatomy, and syphilis give no attention to it.

Rach and Wiesner state that in children having congenital lues who die within the first weeks of life, disease of the great vessels (aorta and pulmonary artery) is one of the relatively frequent findings; but they were unable to demonstrate the presence of spirochetes in these lesions. The writer has seen such lesions in the intima of the aorta and in the endocardium of cases of congenital syphilis in which spirochetes were found in large numbers. These lesions, however, were very different from the arterial changes in adult syphilis; they were primarily colonizations of the spirochetes in the intima resulting in a fibroblastic proliferation of the latter.

Rejecting all but the most probable cases, the reported observations upon the occurrence of syphilis of the pulmonary artery may be classed as follows:

### 1. *Gumma of the Pulmonary Artery*

1. *Weber, 1863.*—Girl, 21 years of age, had been treated for secondary syphilis. Autopsy showed gummata of skull, liver and right pulmonary artery.

2. *Wagner, 1866.*—Male, 31 years old, history of syphilis for eight years, showed at autopsy gummata of myocardium, tongue, pectoralis major muscle, pericardium, skull and pulmonary artery.

3. *Sequiera, 1897.*—Male, aged 37 years, died suddenly, showed at autopsy a tumor in the wall of the pulmonary artery just above the semilunar valves. From its microscopic structure it was regarded as a gumma.

4. *Hanford, 1901.*—Woman, aged 32, with history of dyspnea and fainting attacks, showed at autopsy gummata of the interventricular septum and the wall of the pulmonary artery just above the valves.

### 2. *Gummatous Arteritis of the Pulmonary Artery*

1. *Schwalbe, 1890.*—Woman, 53 years old, had symptoms of palpitation, dyspnea edema and cyanosis for six weeks. Autopsy showed sclerotic changes and multiple small gummata in the pulmonary artery.

2. *Kasem-Beck, 1900.*—Male, aged 50 years, with symptoms of decompensation, showed at autopsy sclerotic changes in the pulmonary artery associated with multiple small gummata.

He refers to a case reported by him in 1889, showing also a gummatous arteritis of the pulmonary artery.

3. *Wagner and Quiatkowski, 1903.*—Male, aged 49 years, with history of untreated syphilis, symptoms of dyspnea, palpitation and general edema. Autopsy showed gummata of the heart, healed gumma in liver, and a gummatous arteritis of the pulmonary artery.

4. *Winternitz and Schmeisser, 1917.*—Two cases reported at the meeting of the International Association of Medical Museums, April, 1917, New York. Through the kindness of Dr. Winternitz I am permitted to make note of these cases, a study of which will soon be published.

Case 1. Male, colored, aged 27 years, had chancre and skin rashes at age of 17. Positive Wassermann. Admitted with symptoms of multiple aneurysms. Autopsy showed syphilitic arteritis of aorta, pulmonary, splenic and right femoral arteries; saccular aneurysms of the arch, descending aorta, splenic and right femoral arteries; fibrous orchitis; syphilitic cirrhosis of the liver; healed gumma (?) of kidney; pseudolobar pneumonia with abscess; fibrinopurulent pleurisy.

Microscopic examination of the pulmonary artery showed a syphilitic arteritis with gummatous areas.

Case 11. Male, colored, aged 56 years, without history of venereal disease, was admitted to Dr. Barker's service in the Johns Hopkins Hospital complaining of "shortness of breath." Two Wassermans were negative. Autopsy showed fibroid induration of lungs; chronic adhesive pleuritis; mesarteritis of pulmonary artery with aneurysm of right main branch; thrombosis of sac; hypertrophy and dilatation of right ventricle; miliary gummata or tubercles of liver; chronic passive congestion; ascites; edema.

Microscopic examination of the wall of the pulmonary artery gave a typical picture of syphilitic mesarteritis with gummatous nodules.

Spirochetes were not demonstrated in either case.

### 3. *Nongummatous Arteritis of the Pulmonary Artery*

In this group can be placed only those cases in which there was a definite probability that the changes in the pulmonary artery were due to syphilis. In the absence of gummatous lesions the observers recording such cases could only assume their syphilitic nature either because of a definite clinical history of that disease or because the pulmonary lesions were associated with well-marked lesions of



syphilis in other organs. The presence of the spirochete pallida in these lesions has not yet been demonstrated in any case. In an analysis of 172 cases of pulmonary arteriosclerosis gathered from the literature Posselt found syphilis to be the most important associated condition in 6.9 per cent. It is interesting to note, however, that myocarditis was the associated finding in 15 per cent of cases, and arteriosclerosis in 12.6 per cent. The importance of syphilis as an etiologic factor in these two conditions enhances its probable relationship to pulmonary sclerosis.

Brüning (1901) thought that it was not improbable that syphilis was of some importance in the etiology of pulmonary sclerosis.

Thorel (1903) stated that the etiology of pulmonary sclerosis remained unsolved if syphilis were not considered.

Henschen (1906) came by exclusion to the hypothesis that narrowing and sclerosis of the pulmonary artery in the majority of cases were due to syphilis.

Rogers (1909) states that in Bengal pulmonary arteriosclerosis is not a rare cause of fatal dropsy, and believes that when it occurs between the 20th and 40th years it is apparently caused by syphilis.

#### *Reported Cases of Syphilitic Pulmonary Arteriosclerosis*

1. *Dickinson, 1862.*—Male, aged 40, with fibroid myocarditis and pulmonary sclerosis.

2. *Payne, 1874.*—Woman, aged 33 years. Sclerosis of pulmonary artery and branches without known cause. Lues (?).

3. *Wallis, 1887.*—Girl, aged 23. Father luetic. Marked hypertrophy of heart with normal valves. Sclerosis of aorta and pulmonary artery. Lues (?).

4. *Friedrich, 1889.*—Case showed gummatous nodules in wall of aorta. Induration of the wall of the pulmonary artery and narrowing its lumen.

5. *Grigorjew, (Cited by Posselt).*—Woman, aged 34, with syphilis and pulmonary aneurysm.

6. *Loveland, (Cited by Henschen).*—Man, aged 51 years, with syphilis and pulmonary aneurysm.

7. *Brüning, 1901.*—Two cases of pulmonary sclerosis associated with syphilis. Male, aged 54, with lues, aortic and pulmonary sclerosis. Male, aged 72, luetic changes in various organs. Sclerotic changes in pulmonary artery.

8. *Wagner and Quiatkowski, 1902.*—Male, aged 49 years, with syphilis, luetic endarteritis of the pulmonary artery, and pulmonary aneurysm.

9. *McPhedran and Mackenzie, 1903.*—Male, aged 55 years, miliary gummata in liver, sclerosis of pulmonary artery, thrombosis, and infarction of right lung.

10. *Ribbert, 1905.*—Case of fatal syphilitic obturation of right branch of pulmonary artery, gummatous aortitis.

11. *Westenhoeffer, 1906.*—Woman, aged 34 years, with extensive syphilis of the arterial system, including the pulmonary artery.

12. *Henschen, 1906.*—Woman 42 years old. No history of syphilis. Myocardial insufficiency and aneurysm of pulmonary artery. Microscopic picture of syphilitic arteritis.

13. *Brooks, 1907.*—Woman, aged 34, who had had one miscarriage, but no other history of syphilis, showed right-sided hypertrophy of heart and extensive sclerosis of pulmonary artery. Syphilis regarded as the most probable cause.

14. *Rogers, 1909.*—Hindu, male, aged 38 years. History and scars of syphilis. Right-sided hypertrophy of heart. Marked sclerosis of pulmonary artery.

15. *Barth, 1910.*—Male, aged 57 years, no history of syphilis. Six years before had slight "stroke." Autopsy showed old pachymeningitis, right-side hypertrophy of the heart, aneurysm of pulmonary artery, and fibrous orchitis. Microscopically, the pulmonary showed changes precisely like those of syphilitic aortitis.

#### 4. *Syphilitic Aneurysm of the Pulmonary Artery*

The literature of aneurysm of the pulmonary artery up to 1909 has been reviewed by Posselt. Henschen, in 1906, had thoroughly sifted and criticized the literature, collecting 42 cases; and Posselt increased this list by nine cases. As mentioned above Henschen, by exclusion came to the conclusion that syphilis must be the most probable etiologic factor in the production of pulmonary sclerosis and aneurysm. Of Henschen's cases of pulmonary aneurysm with arteriosclerosis all with one exception were between the ages of 24 and 42. He regards this as a strong point in favor of syphilis. Of the nine cases added by Posselt six were between 20 and 40 years, and the ages of the other three were 45, 54, and 71 years. Posselt agrees with some reserve to Henschen's opinion, and points out the

necessity of applying the Wassermann reaction and spirochete demonstration to the solving of the question.

#### CASE HISTORY

**HISTORY OF CASE.**—(Medical Clinic of University Hospital: Dr. Foster). Mr. R. McG., aged 37 years, American, machinist.

Family history good.

Patient had measles, mumps and whooping cough during childhood; smallpox in 1907. Has had two gonorrheal infections. Had hard chancre in 1899; for this he received only local treatment. Does not smoke; drinks but little; has generally had very good health.

Patient entered the hospital because of hemorrhage from the lungs. About September, 1916, in the evening he suddenly expectorated about half a pint of blood without any apparent cause. Felt no bad effects. Two weeks after had another hemorrhage of about a quart. This happened at the end of a day's work. He quit work for seven weeks, and during this time he had hemorrhages of 1 to 2 pounds in amount about every four days, even when resting in bed. After returning to work he had hemorrhages also. On December 16, 1916, while working he lost over two quarts. Since then he has done no work. Has had three hemorrhages since January 2, 1917. Has gained in weight during the last four months. Has had no night sweats. Has some hoarseness and cough. Every 2 to 3 hours he brings up some blood-tinged mucus. During the hemorrhages he has some pain through thorax. He has no symptoms of tuberculosis or aneurysm. Sleeps well. Bowels regular.

Physical examination on entrance showed a man of large frame, good nutrition, weight 174 pounds. Musculature is good; panniculus scanty. Temperature 98°. Pulse 90. Respirations 22. Skin smooth, warm, moist, showing few pits from smallpox. Pupils regular, equal, react to light. Accommodation normal. Sclera is clear. Mucous membranes are pale. Tongue protrudes straight, no tremor. Teeth in poor condition. Throat negative. No palpable cervical glands. Diastolic pulsation in neck. Thyroid negative.

*Thorax.*—Inspection negative. No lagging. Percussion negative. Vesicular breath sounds; a few scattered rales on the right lower front. Slight increase in whispered voice over left third and fourth interspaces. Palpation, percussion and auscultation of back negative.

*Heart*.—Apex in 5 i. c. s., half inch outside nipple line; marked diastolic sound in 3 i. c. s., transmitted upwards and across.

*Abdomen*.—Wide epigastric angle. No tenderness. Liver and spleen not palpable.

Radial pulse regular and equal; tension normal. Systolic pressure 130, diastolic 88. Stools and urine negative. Red blood cells 3,950,000; whites 7,300. Slight increase of lymphocytes. One normoblast. Hemoglobin 43.

Reflexes active and somewhat exaggerated on both sides.

No edema. No adenopathy.

Wassermann + + + +

*Provisional Diagnosis*.—Tuberculosis (?); syphilis of the lung (?); weeping aneurysm (?).

*Feb. 2, 1917*.—Diagnosis of syphilis of the lung made, and patient referred to clinic of syphilology for treatment. (Dr. Wile). He had no hemorrhage while in the medical clinic, but shortly after being transferred he lost over a pint of blood. At this time the right radial pulse was noted to be larger and stronger than the left. Patient appeared more anemic. Visible cardiac pulsation five inches to left of midsternal line.

In the clinic of syphilology he received a single intravenous dose of 4 mg. neosalvarsan and daily inunctions of blue ointment. He also received a transfusion of about 300 c.c. of citrated blood following a hemorrhage.

*Feb. 14, 1917*.—Report from department of roentgenology (Dr. Van Zwaluwenburg). "These are very unusual plates. The diaphragm is high, and the density of the lung shadow is apparently great. The left side, however, is denser than the right below the second rib. This opacity is more or less diffuse, especially on the costal margin; and in particular, there is a mass—a shadow—in the left postscapular line, extending from the second to the fourth rib, slightly larger than a hen's egg, fairly sharply defined on its outer border, but poorly defined elsewhere. It seems separated by a small space from another similar shadow occupying the right upper hilus. This chest is so wide that the pleural border is not well shown.

These shadows do not have the characteristics of tuberculosis or of ordinary inflammatory infiltrations. The exact underlying pathology is not discovered. This is suggestive of neoplasm."

*Feb. 16, 1917*.—Physical examination at this time shows marked



Fig. 1.—Roentgen ray plate chest. Shadow of aneurysm shows as a mass, somewhat larger than a hen's egg, on the left extending from second to fourth ribs, fairly well defined on its outer border, but less well defined elsewhere. The density of the lung shadow on both sides is great, but more marked on left below the level of the second rib.



pallor and weakness. Patient is nauseated and vomits after almost every meal. He is markedly dyspneic. There is well-marked edema of the ankles. At the cardiac apex there can be heard a loud rough to and fro murmur, definitely influenced by pressure with the stethoscope, and transmitted all over the left chest and into the axilla. The urine contains about 8 grains albumin per liter, and many granular and cellular casts.

Patient was unable to take much by mouth and was given water by rectum, containing five grains sodium bicarbonate, two grains sodium citrate and one grain potassium iodide to the liter. This was well retained; but towards evening the dyspnea became more marked, the extremities were cold and covered with cold sweat; and the patient complained of dull pain all over the thorax and abdomen. Death occurred at 11:00 P. M.

*Clinical Diagnosis.*—Lues. Gumma of Lung. Anemia.

Autopsy by Dr. Warthin, at 8:00 A. M., 2-17-17. The autopsy protocol is as follows:

#### AUTOPSY PROTOCOL

*General Inspection.*—Length 175 cm. Strong athletic build. Bones large. Thorax large; epigastric angle 180°. Left side more prominent than right, particularly in cardiac area. Musculature well developed; muscles firm. Rigor mortis present throughout. Panniculus is moderate. General edema. Skin pale, discolored over the sternum. Superficial vessels contain little blood. Hypostasis very pale. Mucous membranes very pale. Lips and tongue covered with grayish coating. Teeth poor. Foul odor from mouth. Facies older than of his age. Beard slightly gray.

*Head and spinal cord* were not examined.

*Main Incision.*—Panniculus on section is pale and moist. No gas in the peritoneal cavity. Small amount of clear, amber fluid. Omentum fatty, anemic. Position of abdominal organs normal. Peritoneum clear, moist, shining. Diaphragm on the right at lower border 4th rib; on left at upper border of 7th rib. Costal cartilages cut easily with exception of first on both sides. Sternum rather sclerotic, marrow not hyperplastic. About 300 cm. clear fluid in left pleural cavity; small amount in right cavity. Mediastinal fat abundant, pale, containing pigmented lymph nodes. Thymic fat abundant. Apex behind 7th rib, outside the anterior axillary line.

*Heart.*—Bovine heart, 17x16.5x8 cm. (after opening). Pericardial adhesions on both sides. Intrapericardial tension increased. Fluid increased in amount, cloudy. Pericardial surfaces cloudy, covered with creamy layer of fibrin. Vessels injected. Epicardial sclerosis over anterior wall of right ventricle. Venæ cavæ greatly dilated. All cardiac chambers greatly dilated. Large agonal white clots in venæ cavæ and auricles. Heart weighs 700 grams after removal of clots and blood. Left ventricle dilated; wall hypertrophic, showing diffuse fibroid patches. Endocardium thickened. Papillary muscles hypertrophic, show marked fatty change ("tiger heart"). Wall 17 mm. thick. Right ventricular wall is 7 mm. in thickness, about one-half being fat tissue. Cavity of right ventricle and auricle greatly dilated. Mitral orifice is relatively insufficient; large agonal clots are attached to its flaps, the edges of which show marked sclerosis. Hydrostatic test of aortic valves shows insufficiency. Valve flaps show slight sclerosis; insufficiency is relative. Tricuspid opening admits entire hand, relative insufficiency. Agonal mixed and chicken-fat clots attached to flaps. Pulmonary orifice admits three fingers. Mixed and lardaceous agonal clots in pulmonary artery. Pulmonary artery much dilated and shows marked sclerosis.

*Aorta.*—The ascending portion of the arch is dilated, and shows marked syphilitic aortitis. Linear and irregular fissures with hyaline change, atheroma, and porcelain-blue thinnings of the wall are seen throughout the entire length of the aorta. In the ascending portion there are two atheromatous ulcers.

*Lungs.*—The left lung is free except posteriorly, where there are firm adhesions over a firm mass about the size of a hen's egg, near the root. On section lung shows marked congestion and edema. Weight 858 grams. There is a well-marked induration of the lung tissue. All of the blood vessels are dilated, and greatly thickened. The pulmonary artery is greatly enlarged, as thick as a finger, and when opened shows marked atherosclerosis of its wall, hyaline areas alternating with yellowish plaques. The division to the upper lobe forms a round aneurysmal dilatation, of the size of a guinea hen's egg, nearly filled with a laminated red clot, part of which is old and part more recent. The thrombus is firmly adherent to the wall on the posterior side of the sac. The wall of the sac is directly continuous with the lumen of the artery; it presents the gross appearances of a syphilitic arteritis, in all respects resembling syphilis of the aorta. No break in the sac is present, and no macroscopic hemorrhage is





Fig. 2.—Photograph of left lung showing the opened aneurysmal sac of the main branch of pulmonary artery in upper lobe. Lying in the sac is a laminated blood clot. Just below the aneurysm, to the right of the branches, the slit-open dilated pulmonary artery shows very well the marked sclerosis of its wall. Throughout the entire lung the smaller branches of the arteries show marked sclerosis.



seen about it. The lung tissue about the aneurysm is much compressed, atelectatic, and brownish gray in color. The entire left lung presents the appearance of a very marked chronic passive congestion with sclerosis of the vessels. The right lung is free throughout. Beneath the pleura on the outer surface of the lower lobe there is a calcified healed tubercle. The lung presents the same appearances of a chronic passive congestion with sclerosis of the vessels as does the left. No pneumonic areas in either lung. Anthracosis is marked in areas. The bronchial nodes are heavily pigmented, and on the left are much enlarged, indurated and edematous. *Bronchi* are negative.

*Esophagus*.—Negative.

*Spleen*.—Lower border two finger breadths above edge of ribs. Weighs 275 grams; measures 13x9x6 cm. Plump. Stroma increased. Chronic passive congestion.

*Stomach*.—Marked atrophy of mucosa.

*Intestines and Appendix*.—Negative.

*Pancreas*.—Small, firm. Marked fatty atrophy. Lobules small, well outlined. Consistency firmer than normal, especially towards head.

*Liver*.—Weighs 2600 grams; measures 26x22x11 cm. Still warm. Lower edge smooth. On the anterior surface of right lobe there is an umbilicated depression 4x7 cm. Above this there are a number of smaller depressions. Over these the capsule is thickened. On section the liver surface shows increase of stroma and atrophy of lobules with fibroid areas corresponding to the depressions in the surface. The largest one has a caseous center stained with bile. The appearances are those of a syphilitic cirrhosis with multiple gummata, the majority of these in a healing state. *Gall bladder* and *portal vein* were negative. *Mesenteric lymph nodes* negative.

*Adrenals*.—Both adrenals deeply embedded in fat. Cortical portion shows excessive lipoidosis. Medullary portions show postmortem softening.

*Kidneys*.—The left kidney weighs 600 grams, and measures 17x11x7 cm. Enormous fatty capsule. The fibrous capsule is adherent. Cortical surface smooth; slight fetal lobulation. Few small retention cysts. Kidney very anemic; cut surface cloudy, slight brownish in color. Cortex above pyramids measures 5 to 6 mm. Outlines of labyrinths and medullary rays are not distinct.

The right kidney weighs 550 grams, and measures 16x10x6.5 cms. On section shows appearances similar to those of left kidney.

*Bladder*.—Negative.

*Prostate*.—Negative.

*Seminal Vesicles*.—Negative.

*Penis*.—Genitals large. Scrotum low-hanging. Foreskin tight; large amount of smegma. Shallow ulcerations and erosions over glans and foreskin.

*Testicles*.—Large and firm. On section the right testis shows some fibrosis; the left testis shows larger patches of fibrosis.

#### MICROSCOPIC EXAMINATION

*Heart*.—Fatty infiltration of subepicardial tissue. Early pericarditis. Hypertrophy and atrophy of muscle. Fatty degeneration of papillary muscles ("tiger heart"). Diffuse fibrosis. Active areas of plasma-cell infiltration, syphilitic myocarditis.

*Aorta*.—Advanced atherosclerosis of intima and media. Lymphocyte and plasma-cell infiltrations along vasa vasorum of adventitia and media. Obliteration of the small arterioles. Typical syphilitic aortitis ("mesaortitis"). One of the atheromatous ulcers shows a small attached thrombus and a beginning dissecting aneurysm tear in the intima.

*Lungs*.—Marked brown induration. Great numbers of pigmented "Herz-fehler" cells in the alveoli. Chronic passive congestion and edema. Thickening of alveolar walls, interlobular septa and vessel walls. All branches of pulmonary arteries show more or less sclerosis and are greatly dilated. In the neighborhood of the aneurysm there is marked atelectasis with old and more recent hemorrhages into the alveoli. Hypostatic congestion in both lower lobes. Calcareous tubercle in lower right. No pneumonic areas. No syphilis of lung tissue or bronchi. *Bronchial nodes* are moderately anthracosed. They present a marked new formation of blood vessels with concentric thickening of the walls and obliteration of their lumina. Plasma-cell infiltrations occur about the vessels. Syphilitic lymphadenitis.

*Wall of Aneurysm*.—An old red clot, somewhat laminated, rests upon the hyaline, sclerotic thickened intima of the artery. The thrombus shows but little organization. Secondary atheromatous changes occur in portions of the hyaline intima. The media is al-



Fig. 3.—Photomicrograph of a small pulmonary artery wall (intima side). Marked fibrosis of intima, with small collections of inflammatory cells about the small vasa vasorum. Syphilitic arteritis.

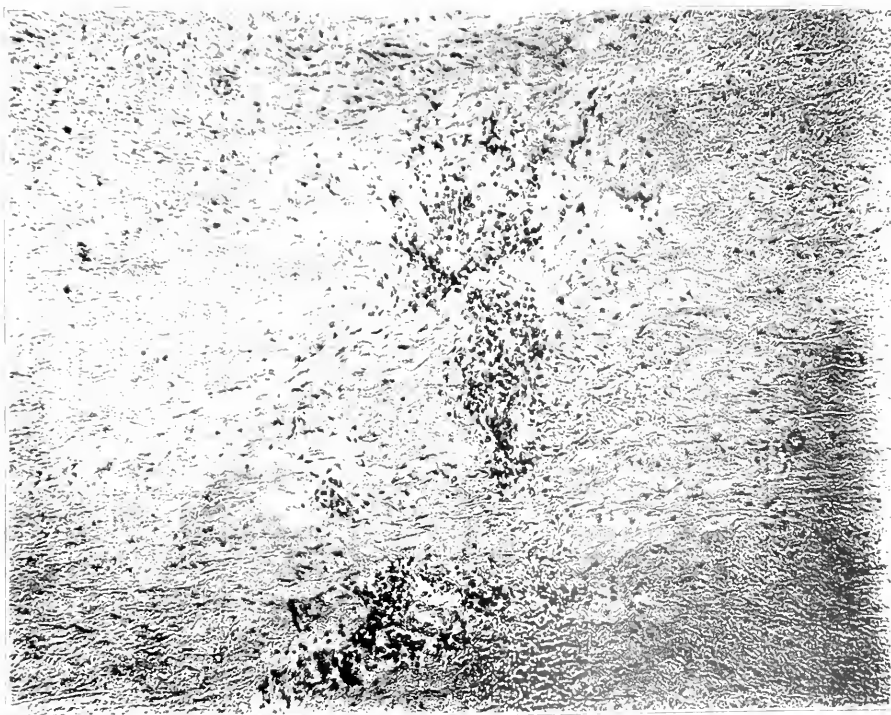


Fig. 4.—Photomicrograph of media of thickened sclerotic pulmonary artery. Typical picture of syphilitic mesoarteritis: infiltrations of lymphocytes and plasma cells along the vasa vasorum; marked fibrosis.





Fig. 5. Syphilitic aortitis of the aorta. Lymphocyte and plasma cell infiltrations in wall of artery at point of branching.



Fig. 6.—Syphilitic arteritis of pulmonary artery: small plasma cell infiltrations; fibrosis; obliteration of one of the vasa vasorum.





most entirely replaced by a dense hyaline fibrous tissue, in which only a few unstriated muscle cells can occasionally be recognized. In this connective tissue there are many new vessels; the arterioles have greatly thickened walls, and many show an active proliferating endarteritis. Around the small veins there are plasma-cell and lymphocyte infiltrations and fibroblastic proliferations, extending along these and the capillaries from the adventitia up through the media to the intima. Small infiltrations of plasma-cells occur throughout the media. The process is precisely the same as that seen in syphilis of the aorta. In the outer portion of the aneurysmal wall compressed alveoli filled with pigmented phagocytes are seen. Outside of these the alveoli are atelectatic and contain more recent hemorrhages. The small bronchi in the neighborhood contain mucus and fresh blood.

*Pulmonary Artery.*—Sections of the sclerotic pulmonary artery and its divisions show a syphilitic arteritis in all respects identical with the process of syphilis of the aorta. The intima is thickened, hyaline, with patches of atheromatous change; the media shows fibroid areas and infiltrations of lymphocytes and plasma-cells extending along the vasa vasorum, these increasing in the adventitia, with proliferating endarteritis of the small arterioles, obliteration of their lumina, fibroblastic proliferation and new formation of capillaries in the vessel wall.

*Spleen.*—Atrophy. Chronic passive congestion. Sclerosis of vessels. Increase of stroma. Hyaline change in some of the follicles.

*Liver.*—Diffuse syphilitic hepatitis, with multiple gummata; some in active stage, others healing. Brown atrophy and chronic passive congestion.

*Pancreas.*—Fatty atrophy. Patches of active syphilitic infiltrations. Acini dilated.

*Intestine.*—Hyperplasia of lymphoid tissue. Subacute catarrh.

*Stomach.*—Subacute catarrhal gastritis. Atrophy. Small plasma-cell infiltrations in subserosa.

*Adrenals.*—Patches of lipoidosis in cortex. Increased pigmentation. Small active syphilitic infiltrations in medulla.

*Kidneys.*—Subacute parenchymatous degenerative nephritis with ascending purulent pyelonephritis.

*Seminal Vesicles.*—Marked pigmentation of epithelium. Hyaline thickening of walls.

*Testis*.—Simple atrophy. Aspermatogenesis. Early syphilitic orchitis, more advanced in left.

#### LEVADITI PREPARATIONS

Levaditi preparations were made of the wall of the aneurysmal sac and of portions of the pulmonary artery below the aneurysm. As the autopsy was performed nine hours after death the conditions were not regarded favorable for a successful Levaditi, although the internal organs were still warm. In five out of fifty sections of the aneurysmal wall undoubted spirochetes of the pallida type were found. In one section three spirochetes were found in the fresh blood clot in the sac, showing the occurrence of the organism in the circulating blood. They were also found in small groups, 3 to 5, in the wall of the sac, towards the adventitia. In the wall of the pulmonary artery they were also found in small groups in the same location. Owing to the length of time postmortem the fixation and impregnation were not as good as we desire; and as no one of the spirochetes lay wholly within one plane the photomicrograph shows only portions of the organisms in one plane.

*Pathologic Diagnosis*.—Syphilis. Syphilitic aneurysm of left upper division of left pulmonary artery. Hemorrhage into lung. Brown induration and edema of lungs. Syphilitic pulmonary arteritis, aortitis, myocarditis, hepatitis, pancreatitis, adrenalitis, orchitis, lymphadenitis, etc. Multiple gummata of liver. Subacute parenchymatous nephritis with purulent ascending pyelonephritis. Old tubercle in right lung. Anemia. Terminal acute pericarditis. General sclerosis and atrophy.

*Summary and Conclusions*.—Up to the present time no positive pathologic evidence of the existence of a syphilitic atherosclerosis of the pulmonary artery has been produced. This case offers such positive evidence; and syphilis of the pulmonary artery is now put upon the same basis as that of the aorta. The microscopic changes in the atherosclerotic pulmonary artery of this case show exactly similar changes to those found in the wall of definitely recognized syphilitic aortas. Given sections of this pulmonary vessel can not be distinguished microscopically from given sections of syphilitic aortas. The evidence here speaks decidedly in favor of the view of the specific nature of this especial form of arterial change. From the writer's experience he believes that *atherosclerosis, either of the ordinary type or of the syphilitic type macroscopically, that shows on*



Fig. 7. Wall of aneurysm in terminal branch of left pulmonary artery. Marked fibrosis and hyaline change of intima and media. In the latter small lymphocyte and plasma cell infiltrations about the small vasa vasorum.

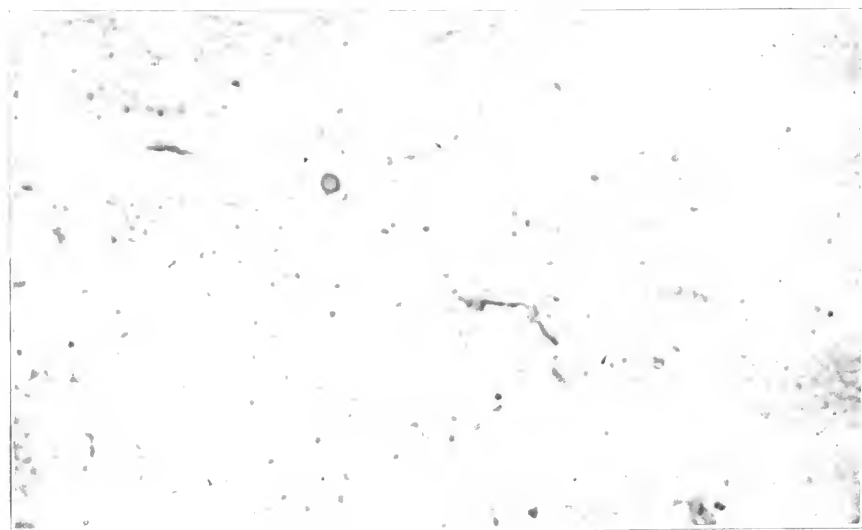


Fig. 8.—Levaditi preparation of wall of sclerotic pulmonary artery. Portions of six spirochetes are seen in the photograph, three near the center field, one at top, one in upper left, and one in left. The two in central field show fairly well. It was impossible to find any spirochetes lying wholly within one focal plane; and these were the only two in which several turns of the organism could be shown in the same focal plane. This field showed unfortunately some precipitate.



*microscopic examination perivascular infiltrations of lymphocytes and plasma cells along the course of the vasa vasorum, most marked in the adventitia; and following the vessels in their course through the media towards the intima, with obliteration of the arterioles, new formation of capillaries, fibroblastic proliferation, fibrosis of intima and media, secondary hyaline change and atheroma is specific in character, and is due to the localization of spirochete pallida along the vasa vasorum.*

Macroscopically the picture presented by the affected artery may be that of ordinary atherosclerosis or of the type recognized at the present time as syphilitic mesaortitis. Syphilis can not be ruled out by the naked-eye appearances of the aorta or artery at the autopsy table; the autopsy diagnosis of syphilis, however, can be made on the macroscopic criteria of syphilitic mesaortitis, as given above. Aortas presenting the gross picture of atherosclerosis may show on microscopic examination the most marked syphilitic infiltrations of the media and adventitia, and in Levaditi blocks from the same the presence of spirochetes has been shown. *The microscopic examination is the only method by which syphilis of a vessel can be determined; macroscopic appearances can not be relied upon.*

The gross appearances of the pulmonary artery in this case were those of atherosclerosis. Had it not been for the aneurysm present its syphilitic nature would not have been sought and demonstrated. The question, therefore, of great importance now is the frequency of syphilitic lesions of this artery. Is it rare, as Winternitz and Schmeisser conclude? Probably not, as a part of the general picture of old syphilis. Many of the slight or moderate scleroses of this artery found at autopsy may prove on histologic study to show active syphilitic infiltrations. These alone could be safely interpreted as syphilitic. Future studies must be relied upon to give us knowledge as to the incidence of syphilitic lesions of the pulmonary and other arteries.

That syphilis of the pulmonary artery and its branches is of great clinical importance does not appear at the present time. In our case it was, being the direct cause of the symptoms and chiefly responsible for the death of the patient. This was due to the fact that the syphilitic disease of the artery had led to the production of an aneurysm of such size as to be of clinical importance; but syphilitic aneurysm of the pulmonary artery would appear to be a

very great rarity from the literature. It is most probable that in every case of syphilis some lesions occur in the pulmonary artery as they do in the aorta; but their clinical significance would be probably only that of a contributory factor to the general cardiovascular disturbances that arise sooner or later in every one who has become infected with syphilis. There is, however, a distinct clinical complex of dyspnea, cyanosis, cardiac enlargement, chronic passive congestion and polycythemia that has been shown in a small number of cases (Mönckeberg, Romberg, Aust, Rogers, Sanders, and Barlaro) to be associated with a marked sclerosis of the pulmonary artery. Barlaro has recently reported a case of this kind in a woman of 44 years. The chief symptoms were marked cyanosis, pulse 80, regular, right heart dilated, red cell count, 6,680,000, attacks of dyspnea about three times daily relieved by expectoration which occasionally gave bloody sputum, general chilliness and coldness of feet. Barlaro calls this condition "Ayerza's disease," and believes that some of the cases reported as chronic polycythemia, "Vaquez's disease," were of this type. He believes that syphilis is probably the etiologic factor. In a case of chronic cyanosis, polycythemia (9,000,000 red cells) and dyspnea, autopsied by the writer a few years ago he found the most marked condition of atherosclerosis of the pulmonary artery and branches. He thought the polycythemia might be purely compensatory for the pulmonary sclerosis. This case is under study and will be reported later.

In conclusion, this case presents a patient with definite history of chancre and skin rashes, with Wassermann + + + +, showing at autopsy syphilitic lesions in heart, aorta, liver, pancreas, adrenals, and testes, and an atherosclerosis and aneurysm of the pulmonary artery in the walls of which *spirochete pallida* was demonstrated. Syphilis of the pulmonary artery and syphilitic aneurysm of the pulmonary artery are, therefore, for the first time conclusively demonstrated as pathologic entities.

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## SOME OBSERVATIONS ON LATENT OR CLINICALLY INACTIVE SYPHILIS IN THE CANAL ZONE

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AT the 115th meeting of the Medical Association of the Isthmian Canal Zone in November, 1915, I read a preliminary report on a Wassermann test survey of colored male employees admitted to the general surgical section of Ancon Hospital. This paper is a continuation of that report, with some comparisons of the percentage of syphilitic infection in white and colored residents of the Canal Zone.

Craig states:<sup>2</sup> "The theory advocated by a few authors that a positive Wassermann reaction is merely an evidence of past syphilitic infection, has been proved to be erroneous, and it is now generally admitted that a positive reaction, if persistent, means the presence somewhere in the body of living spirochetes." Craig further states: "One may go still further as proved by the so-called provocative Wassermann test, that even an evanescent positive result, if obtained after the administration of salvarsan or neosalvarsan, proves the existence of syphilis."

Warthin<sup>3</sup> has shown that "the negative Wassermann reaction can not be taken as evidence of the absence of latent syphilis." He has shown the persistence of living spirochetes in many organs, the patient's blood serum during life giving a negative Wassermann reaction. This is because the Wassermann test, as usually done, is a qualitative and not a quantitative test. It is theoretically, though not practically, possible in this hospital to use a series of antigens of different strengths, and thus detect some weak positive which now escapes detection. Warthin also points out that the general hygiene of the spirochete carrier is probably of as great importance as the general hygiene of latent tuberculosis. This he states is a point not yet sufficiently emphasized in the treatment of syphilis.

Taking these facts into consideration, it is evident that we are much in need of Wassermann test surveys in various parts of the



world and certainly a routine blood Wassermann test on all cases entering the hospital for treatment is one ideal to be attained.

The British Parliament, on Nov. 1, 1913, appointed a Royal Commission for the Investigation of Venereal Diseases. This commission devoted more than two years to the investigation of the subject, and made its report March, 1916. The essential recommendations of this commission have since been enacted into law. The report<sup>4</sup> has been briefly summarized in a recent editorial of the *Journal of the American Medical Association*: "It holds that the registration and medical examination of prostitutes are ineffective as a sanitary measure. It recommends against the compulsory notification of venereal diseases at present. It urges the importance of education as to the seriousness of venereal disease and the dangers of its transmission. It recommends the encouragement of well-considered efforts for inculcating sexual restraint." The commission puts great emphasis, however, on the diagnosis and "therapeutic attack on syphilis and by its recommendation indicates the opinion that in this lies the hope of the sanitary control of the plague."

As far as clinically inactive syphilis is concerned, the Wassermann test upon patients entering our larger hospitals is so far as I know the best and most practiced means at our disposal for the determination of the percentage of syphilitic infection in a given locality.

A physical sign or a symptom presumed to be syphilitic will in a great many cases test the best diagnostic acumen. If in taking a routine blood Wassermann test a double positive is found without positive indications to the contrary, such as a coexisting acute nephritis, not due to active syphilis, persistent anti-syphilitic treatment is surely indicated.

To treat a single symptom or a physical sign without obtaining a Wassermann test and exhausting other means at our disposal for diagnosis unless in case of emergency, is a haphazard procedure. It may not only harm the individual patient, but will mar and tend to discourage and disorganize the modern scheme for its diagnosis, cure, and prevention.

To treat a given positive case of syphilis, especially in those the manifestations of which are not apparent to the patient, a careful and painstaking syphilitic record, not only of the disease, but also of the patient himself, should be kept. This procedure will inspire confidence in the physician, assure active and persistent treatment,

tend to prevent him being a menace to others, and prevent his falling into the hands of quacks. These syphilitic records will also be a library for future reference, stimulating work and thought on this disease. From these records deductions and conclusions may be drawn as to cure or the inability to transmit to wife and offspring, thus making a valuable contribution for our future use. To me at least, it is apparent that one of the chief sources of danger in the transmission of syphilis lies in the clinically inactive syphilitic.

The colored patients on which these tests were performed are natives of the West Indies and are at present residents of the Canal Zone or the adjacent cities of Colon or Panama. The white patients are almost all natives of the United States; a large percentage of these are United States soldiers.

During the past year routine blood Wassermann tests were taken on 1198 colored male surgical cases admitted to Ancon Hospital. These cases were carefully examined physically with a view of separating those with physical manifestations or histories suggestive of syphilis, from those showing no evidence of the disease. From a total of 1198 patients, 901 were classified as nonsuspects, while 297 showed active evidence or gave histories indicating previous syphilitic infection. The double plus reactions among the nonsuspects was 197; the plus reactions numbered 17, giving a total syphilitic infection of 23.7 per cent. The total number of suspects was 297; there were 104 double plus reactions and 5 plus reactions among these suspects, giving a total syphilitic infection of 36.77. From the above data it is seen that the grand total syphilitic infection among all admissions to the male colored surgical wards, is 27 per cent.

The same procedure has been carried out in the white male surgical wards. During the past year 981 blood Wassermanns have been done. The number of double plus reactions was 136. The number of plus reactions 12. This gives a total syphilitic infection of 15 per cent, in cases admitted to the wards. The entire number of cases giving a double plus Wassermann reaction, in which there was no clinical evidence of syphilis, was 23, or 2.3 per cent. A history of venereal sore was obtained in six of these cases, without evidence or history of secondary manifestations.

The results of this work show quite a contrast between the colored and white surgical patients. The total syphilitic infection in

the colored amounting to nearly twice as much—27 per cent as compared to 15 per cent. It is also seen that there is ten times the amount of clinically inactive syphilis among the colored as the white surgical cases—23 per cent as compared with 2.3 per cent.

It is interesting to note that in my preliminary report, based upon 100 Wassermann tests, only 15 per cent of those showing no evidence of the disease were syphilitic, as indicated by the Wassermann test. Among 45 showing evidence of the disease or history indicating infection, 17.7 per cent were infected. This shows the fallacy in taking a small number of tests. However, the proportion of infection among the suspects and nonsuspects remains about the same. I feel that the preliminary report was not in vain. It has been a stimulus to me for further work and apparently an incentive to those in the other wards of this hospital. It also showed conclusively the high percentage of clinically inactive syphilis among the colored surgical patients. This high percentage of latent syphilis among the colored is apparently not due to immunity since the lack of subjective symptoms is seen in nearly all the diseases affecting them.

From a total of 1,198 colored surgical patients on which Wassermann tests were done as a routine procedure, 16 showed albumin and casts to such an extent as to justify a diagnosis of nephritis. Out of a total of 981 white surgical patients, albumin and casts were present in 50. Hence the total number of syphilitics as shown by the Wassermann test, outnumbers by 20 times the clinically non-manifest kidney lesions found in the routine examination of the urine in the colored surgical wards, and by three times the clinically nonmanifest kidney lesions found in the white surgical wards.

The routine Wassermann test showed 27 per cent syphilitic infection in the colored surgical patients, and 15 per cent syphilitic infection in the white surgical patients. A consideration of these results demonstrates the value of the blood Wassermann test in comparison with the routine examination of the urine which, as we know, is carried out in every hospital.

The questions may be raised: "Shall the clinically inactive syphilitic be treated and what can one expect for improvement in the individual patients?" One of the reasons for treatment as has been stated is that it will tend to prevent the transmission of syphilis to wife and offspring. Second: "Who knows what apparently latent constitutional condition we may be treating, whether an incipient

aneurysm, a beginning involvement of the vital centers of the brain, or some other organ, the proper function of which is necessary to health if not to life?" One of these so-called clinically inactive syphilitics died suddenly a few months after discharge from hospital. An autopsy by Dr. Herbert C. Clerk showed a small aneurysm of the ascending portion of the aorta, which had ruptured. The aneurysm gave no clinical manifestations during his stay in the hospital. The cause of admission was contused and lacerated finger. After injury had healed patient refused to stay for the treatment of syphilis. One patient claimed injury to the shoulder, but upon x-ray examination a typical syphilitic periostitis of the clavicle was revealed. Many others showed retardation in healing of surgical wounds, and defective repair in cases of fracture.

Upon 80 of the clinically inactive syphilitics, I kept a careful record after treatment was commenced. Seldom did the Wassermann become negative under two months of active treatment with mercury, by intramuscular injection, and by the use of iodides. By intramuscular injection and inunction it is possible to control the dosage more exactly than when the drug is given by mouth.

It may be stated by some that a routine blood Wassermann, if positive, will tend to discourage a thorough physical examination and thereby result in treatment only of the disease without knowledge of the location of the disease, the condition of the patient, or the presence of other diseases. Such might apply to one not interested, or one with haphazard methods. To the zealous worker, however, the persistent positive blood Wassermann will be a definite indicator of an active pathologic process, and will in some instances even in clinically inactive syphilis, result in its location. Here the words of Osler are most fitting: "Know syphilis in all its manifestations and relations, and all other things clinical shall be added unto you."

There is another large class of cases of latent syphilis of great importance, which will be missed by routine blood Wassermann tests. These are the cases of latent cerebro-spinal syphilis. The great value of the examination of the spinal fluid in such cases has become increasingly apparent to me. The study of the subject is of so much importance that its consideration is reserved for a future paper.

## SUMMARY

1. From a total of 1198 colored surgical patients, 908 showed no evidence of syphilis or gave history suggestive of the disease; 297 showed active evidence of syphilis or gave histories indicating previous syphilitic infection. The Wassermann test survey shows 23.7 per cent of the nonsuspects to be syphilitic, and 36.7 per cent of the suspects to be syphilitic. A grand total syphilitic infection of 27 per cent exists among all colored employees admitted to the surgical wards.

2. The latent syphilitic infection among colored male employees in the Canal Zone is exceedingly high; 23.7 per cent, as compared with the white employees showing 2.3 per cent.

3. The total syphilitic infection among the white surgical patients is 15 per cent.

4. The routine blood Wassermann test is an ideal to be attained in hospital practice.

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## A COMPARISON OF SOME OF THE IMPORTANT PHENOMENA IN SYPHILIS AND TUBERCULOSIS

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INASMUCH as syphilis and tuberculosis are our two best known and most widely distributed chronic infections, it seemed to me that a general comparison and contrast of some of the more important phenomena in the course of the two diseases might be made the subject of a profitable study.

These two diseases have many points of similarity, yet they are widely different in other particulars. They are both chronic inflammatory infections, which, after gaining access to the body tissues, may persist within the body of the host during the remainder of his life, either with or without causing recognizable symptoms. Both diseases are accompanied by toxemia during the period when the specific causative organisms are multiplying; both possess the characteristics of infecting practically all tissues of the body; yet each one has its own peculiarities and each has certain tissues for which it shows predilection.

The greatest similarity in the two diseases comes from the fact that they are both chronic infections, and as such produce changes in the tissues where the specific microorganisms become implanted, from which toxins are given out during periods of activity and from which further spreading of the disease may occur at any time during the life of the host when the biochemical conditions of the tissues become favorable to the infectious microorganisms; and further from the fact that being chronic infectious inflammatory processes which may affect any organ or structure, similar symptoms appear no matter which disease is present. These points will be made clear as our analysis proceeds.

### INFECTIOUS AGENT

The infectious agent in tuberculosis is a rod-shaped bacillus, protected by a heavy coating of wax which makes its destruction in the tissues very difficult. The *treponema pallidum*, on the other hand,

seems to belong to the protozoa and, while tenacious of life when imbedded in the tissues of its host, is very susceptible to the action of certain chemicals, particularly arsenic, a fact which offers hope for the ultimate specific eradication of syphilis from the body. The difficulties surrounding the destruction of both treponemata and tubercle bacilli are greatly increased by the protective cellular wall which surrounds them.

*The Treponema.*—The portal of entry in case of the treponema is nearly always evident, while that of the tubercle bacillus is concealed. The treponema is conveyed through contact, and it is believed that an abrasion in the surface is usually an important factor in infection. Multiplication of the microorganisms takes place at the point of inoculation, forming the chancre and giving what might be termed a primary incubation stage which lasts, on an average, three or four weeks. At the end of this period the infection has extended to the regional lymphatic glands and the second incubation period begins, during which time the treponemata again multiply and prepare for the general attack upon the host. This second incubation period is about twice as long as the first, averaging six to seven weeks. At the end of this time sufficient treponemata have developed to produce a general invasion of the body. They gain general access to the blood stream and are deposited in the tissues throughout the body. They now become implanted in the skin, producing the well-known cutaneous lesions; in the mucous membranes of the mouth and throat, causing mucous patches; and settle more or less generally throughout the tissues of the body.

It seems that, by this time, a considerable degree of specific resistance has been developed by the host, and the treponemata which have heretofore developed freely now grow sparingly and multiply with difficulty. This is evident from the fact that treponemata may be recovered from the various lesions but that the lesions remain more or less abortive in character. A long time may now elapse before the microorganisms are again found multiplying and the inflammatory processes active.

During this period of quiescence, the treponemata are embedded in the tissues living under conditions which they are able to make consistent with life but which are not favorable to multiplication and rapid growth. Renewed activity depends upon the development of conditions more favorable to the invader.

*The Tubercle Bacillus.*—The tubercle bacillus enters the tissues in such a mysterious way, that years of observation have not yet settled the portal of entry. Students are divided in their opinion as to the relative importance of infection through the air passages and the digestive tract; and no matter what theory one supports, he must admit his argument is not conclusive.

The tubercle bacillus does not require an abraded surface for its entrance; in fact, the undenuded mucous surface is accepted as being the most common portal of entrance. When the bacillus passes through the mucous surface, it does not leave a nodule at the point of entrance unless we accept the work of Ghon<sup>1</sup> as conclusive on this point. Ghon shows by postmortem evidence that the lungs of children who have enlarged mediastinal glands always have a primary nodule, often so small as to be overlooked except on most careful search, in that portion of the lung which drains into that particular infected gland. This might be considered as the primary focus conformable to the chancre; except to my mind, as I shall attempt to show, it does not necessarily mark the portal of entry. This splendid work of Ghon is set forth by the adherents of the theory that tuberculosis is an air-borne disease, to show conclusively that the primary nodule must have been formed by bacilli which have entered directly through the air passages.

Against accepting this argument as conclusive, I would call attention to two well-established facts: First, bacilli which are fed to dogs pass through the intestinal mucous membrane, are taken up by the lacteals, carried by the thoracic duct, poured into the blood stream and taken directly to the lung;<sup>2</sup> second, primary nodules are not found in the nasal, or oral mucous membranes, and but rarely in the intestinal walls to mark the point of entrance. The first opportunity for bacilli, entering via the intestines, to become enmeshed in tissues would be in the small blood vessels of the lung. So these primary nodules of Ghon may be due as well to intestinal as to respiratory infection.

In this primary nodule in the body tissues (accepting it as primary, whether the bacilli pass directly by way of the air passages, or indirectly by way of the intestine, thoracic duct, and blood stream), the bacilli multiply in the same manner but probably with less rapidity than the treponemata do in the chancre, and pass on freely as they do into the regional lymph glands where they are held



captive in most instances for a time. From the time the bacilli are first enmeshed in the body tissues, specific cellular defense begins to develop and further inoculation, whether from without or within takes place with greater difficulty.

One of the very evident differences which characterize these two diseases undoubtedly comes from the fact that treponemata develop fairly rapidly after entering the body, while tubercle bacilli develop more slowly.

Within two or three months from the time that the virus of syphilis has entered the body, general dissemination takes place and the treponemata may be found well scattered through the body tissues. Such is not the case generally in tuberculosis. This occurs commonly only in the rapidly disseminating types of the disease as found in very young children. On the contrary, the bacilli which pass from the primary nodule to the regional lymphatic glands are held captive. It is not the rule for them to emerge from the glands and infect new tissues at this time. We may assume that their growth and multiplication in the lymphatic structures is slower than that of the treponemata, also that the cellular wall which they throw about themselves in the formation of the tubercle is more perfect and prevents their ready escape; consequently, a greater specific defense has been developed by the time they are ready to become disseminated.

*Within two or three months from the time that the treponemata become implanted in their host, generalized syphilitic infection is usually present; while years after the tubercle bacillus gains entrance into the tissues, tuberculosis is usually still a localized infection.*

#### CLINICAL DISEASE

Facts concerning immunity in tuberculosis and syphilis are more or less confusing unless one bears in mind that immunity in these diseases means nothing more than an increased resistance to the causative microorganisms. Such a change in the body cells as is noted after measles, whooping cough, and smallpox, which usually makes them uninhabitable for the causative factors, does not exist. Any patient who has once been infected by either the treponema pallidum or the tubercle bacillus may be again infected if the number of organisms gaining access to the tissues be sufficiently large. This is

true both as regards inoculations from without and metastases from some focus within the body.

*Syphilis.*—The clinical course of syphilis shows plainly that a marked defense has developed by the time the treponemata spread from the lymphatic foci. In spite of the fact that they scatter through the body, many of the new foci which result from these fresh inoculations fail to go on to rapidly forming and spreading syphilitic lesions. On the other hand, after the virus scatters and implantation is effected in the various body tissues, there seems to be such a rapid development of specific defense that the treponemata are either destroyed or reduced in virulence and prevented from further activity. If they are to continue surviving the action of the body cells, it is necessary for them to surround themselves with a wall of defense. In this they do much the same as the tubercle bacilli. The wall of cells is more or less avascular and the organisms remain in a condition which is fairly safe from the germicidal action of the body juices. If conditions in a focus ever become favorable to the treponema, a localized active syphilitic process becomes manifest. It is probable that the difference between this late manifestation of syphilis and the early lesions is due largely to the difference in the reaction between the treponemata and body cells which are endowed with specific defense on the one hand and those which are not so endowed on the other. The fact that the activity in tertiary lues is usually in foci in which the treponemata have been a long time embedded is also a factor to be reckoned with.

*Tuberculosis.*—The clinical disease, tuberculosis, if we exclude the acute infection in early life, is a disease which comes on only as a result of repeated metastatic infections. There is, as a rule, no clinical disease evident when the first metastases from the lymphatic glands take place. This occurs at a time which is usually unrecognized because of a failure to produce symptoms. It is probable that bacilli pass into the blood stream at infrequent intervals and usually in small numbers and that only after many repetitions of such occurrences do sufficient bacilli survive to produce a metastatic focus; and the disturbances in body function are so slight that they are usually unrecognized. The term "clinical tuberculosis" is not even attached to the disease at this time. *Only after repeated metastases have formed and recognizable symptoms are present do we consider the infection as a clinical entity.*

# SYMPTOMATOLOGY

In symptomatology these diseases have many points in common. Both are chronic infectious inflammations, which may affect almost any tissue or organ of the body. Being caused by infectious agents and being accompanied by the breaking down of tissue, both are accompanied by the same toxic group of symptoms which are due to not only an increased formation of heat but a decreased elimination caused by the action of the toxins upon the nerve centers. These symptoms are the same whichever disease is present, and no matter in what tissue the disease process is localized; differing, however, in degree, according to the amount of toxin liberated. They are such symptoms as the following:

Malaise,  
 Feeling of being run down,  
 Lack of endurance,  
 Loss of strength,  
 Nervous instability,  
 Digestive disturbances of the type of lessened secretion and lessened motility,  
 Loss of weight,  
 Increased pulse rate,  
 Night sweats,  
 Rise in temperature,  
 Blood changes,

In syphilis these symptoms may manifest themselves very shortly after infection occurs. They are often quite marked during the secondary stage and may occur whenever evidence of increased activity is present. In tuberculosis they do not occur as a rule until metastases with repeated extension have taken place and a focus of considerable size is the seat of active disease. This is usually years after the bacillus has gained entrance to the body.

Every important organ that is involved in an inflammatory process causes reflex symptoms in other organs. These reflexes depend on the fact that the nerves which supply the organ are irritated by the inflammation. For the principal internal organs, such as the lungs, heart, intestines, liver, pancreas and kidney, in each case both the *greater vagus* (Eppinger and Hess)<sup>3</sup> and sympathetic nerves are irritated, and reflex symptoms may appear in many other organs

through the former, and in the skeletal structures, muscles, subcutaneous tissue and skin, which are innervated by the segments of the cord which receives afferent impulses from the inflamed organ through the latter.

#### GENERAL CLINICAL CHARACTERISTICS

Syphilis and tuberculosis are each able to infect any tissue of the body but each shows predilection for certain structures. The lymph glands receive the virus early; and it is in these structures that the treponemata and bacilli multiply before making a massive attack upon the host. Owing to this fact, both of these diseases are spoken of as being primarily lymphatic infections. These lymphatic infections result from the fact that the virus drains into the lymph glands from the primary portal of entry, they having the purpose of receiving and the power of destroying microorganisms which attempt to invade the tissues. Their infection is evidence of the fact that the amount of virus was greater than they were able to cope with. We must assume that microorganisms gain access to the lymph glands more or less frequently during life but are destroyed by defensive forces which are stationed there.

Both treponemata and bacilli gain access to the blood stream now and then during the course of the disease. Treponemata are found in the blood under a great variety of conditions; and far more commonly than tubercle bacilli.

The blood vessels are attacked commonly in syphilis, the treponema penetrating and infecting the walls. This is not common in tuberculosis; the vessels are penetrated, but rarely infected except as they take part in the process about an inflamed tubercle.

Syphilis is then, as a rule, a more generalized infection throughout its course, than tuberculosis. *Infection of many body structures at one time rarely occurs in tuberculosis, except as one of the manifestations of the later stages of the disease, while it is the rule in syphilis from the time of the first escape of the treponemata from the lymphatic glands.* When bacilli escape from the lymphatic glands it is usually to form only a single metastasis.

It seems that two factors stand out plainly as markedly influencing the character of these two diseases, making the one a generalized infection from the time it leaves the lymphatics, and the other a localized metastasis until late in the disease. For some reason the treponemata are not acted upon so adversely by the lymph elements as the bacilli

are. Infection being more direct the number of infecting organisms is probably greater. They develop more quickly, escape sooner, and infect the tissues of the host generally before the tissues have developed a specific defense. Retardation of growth and a tendency to localize the infection does not show itself until many tissues have been infected. In tuberculosis, on the other hand, a marked defense develops before the bacilli leave the lymph glands; in fact, this is usually so potent that it is able to prevent metastases from taking place until a long time, often years, after the lymph glands develop their infection. Another factor which seems to alter the two pictures is the behavior of the two infectious agents toward the blood vessels. In syphilis the treponemata, gaining access to the blood stream before a strong immunity has been developed, enter the coats of the vessels and surround themselves with conditions favorable to their existence; and while they may not go on at once to multiplication and the production of active disease, they do so at the first opportunity whether it be months or years later. Tubercle bacilli, on the other hand, do not escape in large numbers until the body cells and body fluids are endowed with specific protective properties; consequently most of the escaping bacilli are destroyed, and it is only now and then that conditions are exactly right for an infection to occur; and then the metastasis is usually single and not multiple.

The effects of the two diseases upon the central nervous system are very different. Syphilis invades the central nervous system as a chronic, slowly developing, progressive infection, producing organic changes which lead to loss of function. The meninges, and brain and cord substance, and the nerves themselves may be involved. This infection often starts in the blood vessel walls. Tuberculosis, on the other hand, rarely affects these structures except secondarily, and then only if a blocking of the bacilli in the vessels takes place or if some condition favorable to their penetration of the vessel walls exists. When it does occur, it usually produces an acute process, which goes on to a rapidly advancing clinical disease, although now and then quiescent and healed tubercles are found in the meninges and brain.

A way in which these two chronic infectious inflammations affect the nervous system similarly is through their toxins. The unstable, inefficient nervous system possessed by patients suffering from syphilis and tuberculosis (neurasthenia) is well known. The toxins act

centrally and produce an unstable nervous equilibrium. The threshold of response of the nerve cell is lowered and a general instability of action results.

The expression of toxins is most marked through the sympathetic nervous system<sup>4</sup> and results in a general inhibition of action throughout the digestive and respiratory tracts, and the secretory glands in general. Those glands which are normally stimulated by the sympathetics respond, however, with increased activity. This is shown by an increase in adrenalin, a forcing of glycogen from the liver, and an increased activity on the part of the thyroid. The heart beat is increased. General vasoconstriction results which interferes with the elimination of heat and a rise of temperature sometimes results. The symptoms produced by toxins are tabulated above.

#### DIFFERENTIAL DIAGNOSIS

Inasmuch as the two diseases are both chronic infectious inflammations, it can readily be understood that there might be considerable difficulty in differentiating between them when they involve a given organ. This may be illustrated by the processes as they affect the lung. Both syphilis and tuberculosis of the lung during activity produce exactly the same group of toxic symptoms. These have been mentioned above. Since both affect the same nerve endings, they produce the same reflex symptoms in other organs through the pulmonary vagus and in the skeletal tissues through the sympathetics:

Hoarseness,  
Tickling in larynx,  
Cough.

Digestive disturbances: hypersecretion and hypertonus in the muscular coat often resulting in spastic constipation and intestinal stasis,

Loss of weight,  
Circulatory disturbances,  
Chest and shoulder pains,  
Flushing of face,  
Apparent anemia.

Being inflammatory processes in the pulmonary tissue, the same symptoms may result from the disease processes themselves:

Frequent and protracted colds (tuberculous or syphilitic bronchitis),  
 Spitting of blood,  
 Pleurisy,  
 Sputum.

We are aided in diagnosing tuberculosis by finding tubercle bacilli in the sputum if the disease has reached the open stage. The fact that a person having a pulmonary lesion reacts to tuberculin in one case and gives a positive Wassermann reaction in the other, does not prove that in the one case the pulmonary lesion is tuberculous and in the other syphilitic. Data of this kind must be utilized with great care in forming an opinion. When conditions are found, however, which simulate pulmonary tuberculosis, the predilection which the tubercle bacillus shows for pulmonary tissue and the comparative infrequency of syphilitic infection of the lung should cause one to assume that the process is tuberculous unless definitely proved otherwise.

The same general statement may be made with regard to other organs. A laryngeal involvement suspicious of either syphilis or tuberculosis, if secondary to open pulmonary tuberculosis, should be considered as being tuberculous; otherwise syphilitic, although it may be a double infection. Intestinal involvements secondary to open pulmonary tuberculosis, should be considered as being tuberculous. Lesions of other viscera, when open pulmonary tuberculosis is not present, are usually more apt to be syphilitic in character. It is common for syphilis to affect organs other than the lung, while it is comparatively uncommon in adults for tuberculosis to do so except after an open pulmonary lesion has existed for a long time. Differentiation here is aided by the Wassermann reaction. *Syphilis affects the arteries commonly while tuberculosis affects them rarely. In fact, syphilis shows as marked a predilection for the arteries as tuberculosis does for the lungs.*

#### TREATMENT

In comparing the treatment of syphilis and tuberculosis, we find the key to the difference in the attitude of the members of the profession toward these two diseases. The profession as a whole is interested in syphilis, while comparatively few show a vital interest in tuberculosis. *In syphilis measures for treating the disease predom-*

*inate, while in tuberculosis reliance is almost exclusively placed on measures directed toward the patient.* In syphilis reliance is placed mainly in remedies to destroy the treponema pallidum, such as mercury and arsenic, which may be used with a fair degree of success by physicians generally. In tuberculosis there is no known remedy which has a marked antibacillary action and the best known and most widely utilized measures are those which build up the patients' general resisting power, such as open air, light, rest, exercise, food, cheerful and optimistic environment, and remedies which relieve distressing symptoms and complications, which are more difficult to apply successfully because they presuppose an intimate and effective control of the patient. In syphilis much more attention should be given to the treatment of the patient who has the disease; while in tuberculosis, search for remedies, with antibacillary action should continue, so that these two diseases may be approached from the standpoint of both the disease and the patient, and thus make their future treatment far more successful than it is today.

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## THE BEHAVIOR OF THE LYMPHATIC SYSTEM IN SYPHILIS

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THE symptoms of a bacterial disease are those of inflammation modified by the physiology of the organ attacked and by the nature of the attacking virus. In the present discussion the virus is the *treponema pallidum*, and the system is the lymphatic system.

### THE BLOOD VASCULAR SYSTEM CONTRASTED WITH THE LYMPHATIC SYSTEM

The main circulatory system of the body consists of the arteries, of the veins, of a connecting capillary network, and of a propelling organ, the heart. Besides this great circulatory system there is a subsidiary one, a side line, called the lymphatic system.

In the blood system the two circles, the pulmonary and the general systemic, are complete. The current is very swift, and therefore the quantity of blood sent around each circle is very great, over half a ton in twenty-four hours. The conveying tubes are free of impediments, and the fluid involved contains bodies, red blood corpuscles, especially adapted for carrying a heavy charge of oxygen—even the blood serum carries a decided quantity of this gas.

The lymph is distinguished by its sluggish current, and therefore by the relatively small quantity of the juices of the body returned to the central organs by its stream. The total amount of lymph and chyle combined passing through the large vessels in twenty-four hours is only two pounds, and by far the larger part of this is chyle. The quantity of lymph, therefore, draining even from an entire limb is very small indeed. The lymphatic vessels are also remarkable by having along their course cellular nodes, called lymphatic glands, which still further retard their slow current. The lymphatic system consists of two main side lines, neither of which constitutes a complete circle, and the lymph does not, as a system, come in close contact with the air as does the blood, and does not contain red corpuscles, and therefore carries a relatively low charge of oxygen.

The lymph radicals are the spaces between the strands of tissue and even between the cells, and this latter fact is one of peculiar interest in the present discussion, as almost the sole situation for the inoculation of the syphilitic virus is into the rete malpighii of the skin and the mucous membranes, an organ absolutely devoid of blood vessels and rich in lymphatic spaces, as the spaces between the prickle cells are really lymphatic radicals.

#### THE DISEASE-PRODUCING SPIRONEMATA

There are two great classes of spironemata, which infect the human being; those which primarily enter the blood, and those which primarily infect the lymphatic system and tissues.<sup>1</sup> In the first class, such as European relapsing fever and the African tick fever, the infective agents are conveyed by insects, such as ticks and lice, and give rise to short, sharp, febrile diseases, while in the others, represented by syphilis and yaws, the virus is conveyed directly from person to person, and causes slowly pacing tissue diseases with a relatively low fever, or no fever at all.

Although the natural habitat of the *treponema pallidum*, the virus of syphilis, is in an animal (man) with a highly developed oxidizing system, it is especially sensitive to oxygen. This is well shown in cultivating the microorganism, which, mainly on this account, is a most difficult procedure. Great care must be taken to exclude all the oxygen possible, and in addition to this it is found advisable to add a piece of fresh tissue to the culture medium so that, by its continued vital action, the last faint traces of free oxygen may be abstracted.<sup>2</sup>

As before indicated, the *treponema pallidum* is almost always inoculated into the mucous layer of the skin or mucous membranes. One reason for this is that as a contact disease, the skin and mucous membranes, constituting the covering of the body, are the only parts in two persons which can, under ordinary circumstances, come into mutual contact. The situation, therefore, of this mucous layer favors the incidence of this particular virus. In addition to this the virus here encounters a succulent layer, unprovided with blood vessels, and provided with particularly wide intercellular lymph spaces, between the prickle cells, filled with a stagnant lymph. Possibly nowhere in the body is there a situation more favorable for the growth of an anaerobic microorganism. It may be that the tissue

immediately outside the caliber of the blood vessels is approximately as favorable.

#### THE INVASION OF THE BODY BY THE *TREPONEMA PALLIDUM*

The initial local dispersion of this virus must be quite rapid as it has been found useless to excise the site eight hours after inoculation (Neisser). This may be due to the motility of the tenuous organism swimming freely in the large stagnant lymph spaces.

The virus is distinguished by its great adaptability to the race (mankind), which constitutes almost its sole host, its great tenacity and its low obnoxiousness. It is so adaptable that almost no one, not previously infected, is immune; it is so tenacious that only in rare cases, without extraneous aid, is it eliminated; and its individual obnoxiousness to the tissues must be very low indeed, as it requires three or four weeks, even when primarily inoculated, to produce a demonstrable lesion, the chancre. The production of this chancre is a sign that the treponemata, which have invaded the sub-jacent lymph lakes in the connective tissue, have there formed a large colony.

The chancre really is a syphilitic papule and ordinarily the largest one produced in the individual infected. This is an immunity phenomenon, and is a measure of the relatively uncontrolled activity of the microorganisms pullulating in virgin tissue. The treponemata give rise to a particularly dense, nodular, round-celled infiltration, which may be presumed to be fairly oxygen-tight. As a consequence of this the nutrition of the top of this nodule, that part farthest removed from the blood supply, breaks down into an ulcer. It is interesting to note that it is in the lymph from this lesion that the treponema is most easily demonstrated.

Leading out from this primary lesion there sometimes is formed a palpable hard string in one of the lymphatic vessels. It is never more than a few centimeters in length, and it is interesting because it is a symptom of syphilis in the early stages of the disease when the diagnosis is often difficult, and because it is still another indication of the affinity of the virus for the lymphatic system. Coincidentally with the development of the initial lesion the nearest lymphatic nodules lying in the stream draining the infected area, become slowly and indolently enlarged. This enlargement usually involves a number of nodules, one of which is almost always more

enlarged than the others. This is presumably also an immunity phenomenon, as the first gland affected is less immune than the others, and consequently reacts more strongly to the virus. In the meanwhile the virus proceeds slowly along the lymph current, and even may give rise to another string-like induration on the up stream side of the first affected glands.

When the virus is inoculated in the usual situation, in the privates, it ascends to the groins. Of this there is positive knowledge as the treponemata have been found in these lymphatic glands. The natural course would then be for the virus to run onward in the lymph stream into the iliac lymphatics and receptaculum chyli.

The receptaculum chyli is only partially a lymph stream, it is also a fat stream, through which the fat gathered in the intestines is poured into the venous system. The quantity of the juice is relatively, therefore, very much greater and the current is very much swifter than in the peripheral lymphatics. This increase of speed due to increased quantity is accelerated also by the peristaltic and rhythmic contractions of the bowels, and probably also by contractions of the receptaculum chyli itself.<sup>3</sup> It might therefore be presumed that the treponemata would now be poured from the receptaculum chyli in great numbers and swiftly into the venous blood, and passing through the heart and lungs would enter the arterial system to be embolically scattered by it over the entire body.

We have no right to assume that the treponemata in their journey toward the central organs are entirely confined to the lymphatic system, in fact it is known that they are not so confined, as spirochetes have been found in the blood coincident with the appearance of the chancre (E. Hoffman). The lymphatic radicals constitute an open free network consisting of the spaces between the cells and between the tissues, and the treponema is a most tenuous, corkscrew-shaped, motile microorganism, well adapted for insinuating itself between the cells, so that swarms of them must be continually crossing the blood capillaries.

Not only do they enter the blood current because of their insinuating nature, but the currents of the tissue juices must favor this, as the quantity of fluid sucked up from any given locality by the capillaries and the veins must be very much greater than by the lymphatics. This is seen in giving hypodermic injections. If the drugs in these had to await the slow movements of the lymph their

general effects would take hours, not minutes, to manifest themselves. All along the lymphatic track pursued by the invading treponemata there must be this continual effort to invade the blood through the thin-walled lymphatic vessels. The blood, however, so inimical to the invaders, must keep the main body in the lymphatic vessels. It would therefore seem probable that the vast mass of the treponemata which enter the blood for general distribution do so by way of the great lymphatic trunks. After having passed through the heart, these anaerobic microorganisms still must encounter a formidable obstacle in journeying through the lungs, the juices of which are so rich in very active oxygen.

The symptoms of the reaction of the blood against the treponema are those of the prodromes of the stage of the second incubation—they are malaise, a feeling of being weak and tired, pains in the joints, headaches of a boring character occurring especially at night, anemia, a slight or more marked rise of temperature. Frequently these symptoms cease on the outbreak of the eruption. These prodromal symptoms are especially marked in women, in whom they occur in nearly half the cases.<sup>4</sup>

It is interesting to speculate if this strong reaction of the blood in women may account for their greater freedom from diseases of the central nervous system. I have thought also that the greater activity of the thyroid gland in women, presumably giving rise to more iodothylin, might also contribute to the resistance of the blood and to its effectiveness as a shield for the nervous system. Difference in treponema strain would account for differences of incidence of nerve implication in different groups of people having syphilis, but would not account for the striking difference in these lesions as seen in men and in women, because the treponema strain no matter what its proclivities would be common to both sexes.

THE SLOW PROCESS OF THE DISEASE AN EVIDENCE THAT IT INVADES BY  
WAY OF THE LYMPHATICS

The long time which elapses between the appearance of the chancre and the appearance of the first generalized eruption on the skin is of much interest in the present question. It is definitely known that this eruption is caused by the deposition of the treponemata in the skin. These treponemata are supposed to be caught in the capillaries in the great arterial dispersion, and as the original

focus of the disease lies in the periphery they must enter the arterial system through the venous system or through the lymphatic system, the only two systems which drain the juices from the periphery.

From the history of the development of the chancre it is known that it takes from two to three weeks for treponemata deposited in the tissues to produce an appreciable lesion. It is, therefore, fair to assume that the treponemata deposited in the skin in the first great dispersion of the virus take an equally long time to form the roseolar rash. Consequently this time must be deducted from the six or eight weeks which elapse between the chancre and the roseola, and the remaining four or five weeks would represent the time consumed by the virus in progressing along the lymphatic system prior to being poured into the blood current in sufficient numbers to form the first great dispersion.

This long time is required for a generalization of the virus, and the speed of the generalization when once begun, as shown by the wide extent and by the even development of the eruption, would indicate that there is an initial slow centripetal conveyance by way of the lymph stream, and a later rapid centrifugal one by way of the blood stream.

THE CONTINUED SUSCEPTIBILITY TO TREPONEMAL ATTACK OF LYMPHATIC  
TISSUE DURING EARLY CONSTITUTIONAL SYPHILIS, AND ITS  
LATER FREEDOM FROM INVOLVEMENT

As we have seen the treponemata are thrown into the arterial system and are then distributed to the papillary layer of the skin, giving rise to the eruptions of early constitutional syphilis. Why these microorganisms, which evince such a dislike of oxygen, should suddenly settle in an organ, the papillary layer of the skin, particularly well supplied with oxygen, is one of those curious relative affinities so frequently seen in parasitism. Coincidentally with the primary eruptions, however, the treponema continues to show its affinity for lymphatic tissue. The general subcutaneous lymphatic nodules are found to be palpable coincidentally with the first cutaneous eruption and the presence of a Wassermann reaction. Those of the groins, the posterior occipital region, and those lying along the posterior edge of the sternocleidomastoid muscles, and those at the bend of the elbows, the epitrochlears, are especially apt to be

swollen. The swelling of the nodules in the neck may be partly due to a papulo-pustular syphilide of the scalp, a frequent eruption.

The tonsils, the adenoids, and Payer's patches are all of them lymphatic tissue; of these the tonsils are certainly susceptible of the other two we are not so certain.

The inflammations in all these lymphatic structures subside without undergoing suppuration, and subsequently the lymphatic nodules, which are attacked so early and so acutely by the disease, remain particularly free from trouble. Late gummatous and diffuse syphilitic enlargement of the lymphatic nodules does occur, but it is rare. Its recognition is important, however, as it may be mistaken for Hodgkin's disease. This freedom of the lymphatic tissue in late syphilis may be an immunity phenomenon, resulting from the early diffuse infection.

#### SYPHILIS IN THE FETUS AS INDICATING THE IMPORTANCE OF A LOW CHARGE OF OXYGEN ON THE COURSE OF THE DISEASE

In the fetus the usual distinction between arterial and venous blood can not be made, and in no situation is the blood of the fetus up to the arterial standard of the mother.<sup>5</sup> It is well known how luxuriantly the *treponema pallidum* grows in the fetal body juices, and it is not unfair to assume that this luxuriant growth may be partly due to the low charge of oxygen.

#### VALUE OF GLANDULAR ENLARGEMENT AS A SYMPTOM

It is now profitable to consider the above events in regard to their value as symptoms.

The individual spirochete is not quickly nor virulently obnoxious to the tissues. It takes a long time, more than two weeks, during which they multiply into a numerous colony, before they produce a Hunterian chancre. The ulceration of the top of the chancral papule is not purulent. The surface is gray or light red, and secretes a sanious pus. The process looks more like necrobiotic death from strangulation of nutrition due to the tightly packed inflammatory infiltration than as the result of bacterial virulence.

The tightly packed infiltration, which gives rise to the induration, would seem to be a defensive effort on the part of the micro-organism to guard itself against the intrusion of the obnoxious oxygen. This induration is a symptom common to all the lesions of

syphilis, and constitutes one of its most important clinical signs. It is present in the chancre, in the indurated lymphatic cord occasionally found leading from the chancre, in the lymphatic glands which are markedly indurated and which are said to be "indolently enlarged," and in the papules of the secondary eruption, and those also of late syphilis.

Sometimes there is very little or no induration at the base of a chancre, and the ulcer is steep-edged or the edge may be undercut and the floor may be yellow and necrotic. In such a case the chancre in its appearance is indistinguishable from a chancreoid. These differences may be due either to differences in spirochetal strain or to differences in resistance in the patient.

At one time in the history of medicine there was an acrimonious polemical controversy between the dualists, those who held that there were two venereal sores, a chancre and a chancreoid, and the unicists, those who held that there was but one, and that that one was the initial sore of syphilis. The cause of the controversy was, as in all such cases, insufficient knowledge, and it led one of the keenest witted of the controversialists, von Zeissl, to assert that in an initial lesion of syphilis there is always a certain hardness, even though it might not be appreciable to the finger. If not to the finger with what could it have been appreciated!

The "substance" or "body" present in the skin lesion is a most valuable clinical symptom of syphilis. In my student days I well remember a celebrated syphilographer saying that even if he became blind he thought he might still pursue his vocation successfully by diagnosing syphilitic cutaneous diseases by the sense of touch alone.

Although it is probable that all of the six or seven hundred lymphatic glands of the body become affected during the early stages of the generalized infection, yet it is only a few of these which may be felt and which therefore are available for diagnostic purposes. The relative value also of those which are attainable also varies. As previously mentioned, the first lymphatic nodule encountered by the virus is unusually severely affected, and becomes much larger than the others. This is a valuable aid in the search for an occult chancre lying in the drainage area of the enlarged lymphatic gland. Recently a man called at the office with an unaccountable roseola. The submental lymphatic nodule was remarked



as being unusually large, and then two distinct flattened out chancre sites were found just under the chin in the shadow where they were unobservable except on tipping up the head. Chancre of the tonsil gives rise to enlargement of the lymph node just behind the angle of the lower jaw. Chancre of the anus causes enlargement of the lymphatics of the groins, whereas chancre of the neck of the uterus does not do so, as these lymphatics drain into those of the posterior abdominal wall.

Because of the frequency of enlargement of lymphatic glands in normal individuals there has been a strong tendency to belittle its diagnostic value in syphilis. Friedlander's investigations, however, show that glandular enlargement is decidedly more frequent in those suffering from early constitutional syphilis, and that this is especially true of the epitrochlear lymphatic nodules.<sup>6</sup>

Laying aside the importance of this glandular enlargement as a diagnostic aid, there is no doubt of its value as impressing the patient with an appreciation of the seriousness of his trouble. Often he will be more impressed with this symptom as indicating a deeply seated constitutional disease than with any of the eruptions, no matter how striking. And this event occurs at a time when the cooperation of the patient with the physician in carrying out a strictly regulated treatment is often of the utmost importance.

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## SYPHILIS OF THE LIVER

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THE frequency with which syphilis of the liver is met in the practice of medicine is a point of discussion by various authors. In our own clinics it is an extremely common disease, particularly among negroes, as shown from the fact that of 1,200 syphilitics admitted during recent years it was diagnosed clinically 64 times. Moreover, among 1,000 autopsies done upon all classes of patients, 90 cases showed definite cirrhotic changes in the liver which were probably of syphilitic origin as judged by gross and microscopic appearance of the livers, making an incidence among all patients coming to autopsy of about 9 per cent. Of these 1,000 cases, approximately, 300 were syphilitic as judged by autopsy findings, an incidence of disease of the liver among syphilitics of about 30 per cent.

### PREDISPOSING FACTORS

As already mentioned, heredity may play an important part in syphilis of the liver, congenital syphilis being a not uncommon cause of the disease. All of our cases were, however, apparently of the acquired type.

Chronic alcoholism has been suggested as a predisposing factor in liver syphilis by some authors. While our own records regarding the consumption of alcohol in cases of syphilis of the liver show that almost all such cases observed in this clinic have been users of alcohol to some extent, it is found, nevertheless, that almost all of the patients, among the same class, admitted for other diseases, are addicted to the use of alcohol to a greater or less extent. It would seem, therefore, that the cases diagnosed as liver syphilis are not any more addicted to alcohol than are other patients of the same class.

## PATHOLOGY

*Acute Hepatitis.*—The great majority of cases of syphilis of the liver met with clinically are of a more or less chronic nature and represent the manifestation of the tertiary stage of the disease. It is believed by most men, who have been closely associated with syphilis in the practice of medicine, however, that an acute hepatitis or cholangitis may be caused by syphilitic infection. Numerous such conditions have been reported as occurring in syphilitics, such cases usually occurring during the secondary stage of the disease, or at least within a few months of the original infection. Since individuals affected with this stage of syphilis rarely die, however, pathologic specimens of liver showing the lesions of the condition are extremely rare. Numerous specimens of syphilitic hepatitis occurring in infants dying from congenital syphilis have been reported, and it is probable that the lesions in this and the acquired type are more or less similar. Such lesions consist, in the case of congenital syphilis, of a diffuse pericellular infiltration of the parenchyma, chiefly with mononuclear cells. Fibroblasts may be noted. The liver is larger than normal. A cholangitis may also be present.

In spite of the lack of pathologic proof as to the specific changes in the liver parenchyma, giving rise to the enlarged and frequently tender liver occurring during the early stages of syphilitic infection, there is an abundance of clinical evidence in favor of a hepatitis as the cause. Our own series of cases contains seven in which this condition was diagnosed clinically. All of these patients showed definite hepatic enlargement and four showed jaundice. In all, the disease was of an acute type. Moreover, all showed a four plus Wassermann reaction and, finally, all except one, mentioned below, recovered promptly and completely upon specific treatment. Of these cases, moreover, three admitted primary lesions as occurring respectively six months, six weeks, and two months previously. The other three denied primary lesions. In none of these cases was a secondary eruption present at the time of treatment. It seems probable that such acute cases as these are really the precursors of the more serious gummatous and fibrotic changes which take place during the later stages of the infection.

We were fortunate in being able to obtain an autopsy upon one of the above cases diagnosed as hepatitis. This was a negro man

thirty-five years of age who entered the hospital complaining of chills, fever, and pain in his abdomen. There was slight jaundice. The duration of the disease was two weeks. Upon examination the lower border of the liver extended to within two fingerbreadths of the costal margin and tenderness on pressure over the liver was noted. There was also evidence of endocarditis. In spite of the fact that the patient denied lues, the Wassermann reaction was strongly positive. The patient was accordingly placed upon vigorous antisypilitic treatment which was followed by prompt and marked diminution in the size of the liver, with some improvement in the general condition of the patient. Fever and chills continued, however, and the patient finally died after an illness of five weeks. Autopsy showed a malignant streptococcic endocarditis with multiple pulmonary infarcts as a cause of death. The liver was most interesting, being still slightly enlarged and cutting with ease. The cut surface was apparently normal upon gross examination. Microscopic examination revealed an interesting condition, however, since the whole liver parenchyma was diffusely infiltrated with small round cells. In addition, many collections of such cells were noted (Fig. 1) within which one or more giant cells could be distinguished. Evidently these represented miliary gummata in process of formation. A proliferation of fibroblasts was also noted. Evidently, therefore, we were dealing with an early case of syphilitic hepatitis.

*Cirrhosis.*—The later stages of syphilis produce changes in the liver which are much better known than those described above. Pathologically, such lesions correspond closely to those caused by syphilis elsewhere in the body, gummatous and fibrotic changes playing the chief part in the picture. Grossly the syphilitic liver may be divided into three general types: 1. The lobulated liver, (*hepar lobatum*). 2. The diffusely cirrhotic liver. 3. Syphilitic perihepatitis.

Frequently all of these three types are found in the same liver, although pure examples of any one type are not uncommon.

The *lobulated type of syphilitic cirrhosis* is often characterized by the presence of gummata. The more or less characteristic lobulations of the parenchyma are produced by the formation of cicatricial tissues as the result of absorption of gummata and their replacement by fibrous tissue. The liver may be divided into a number of

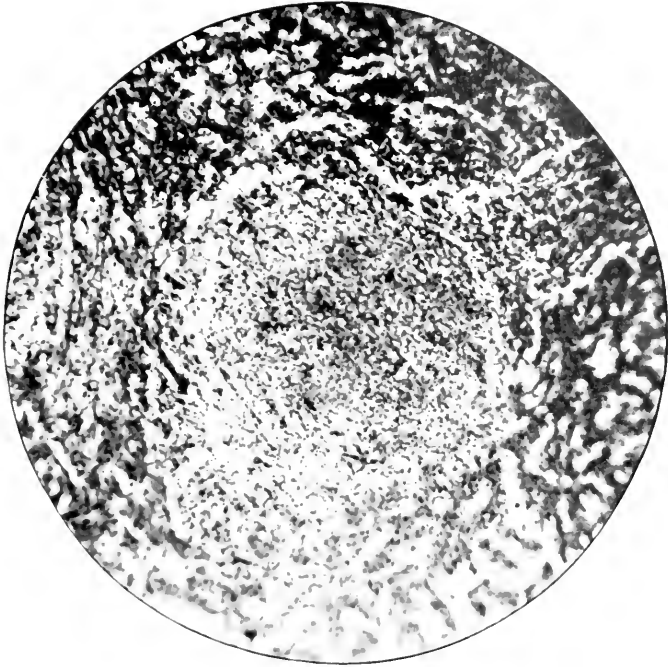


Fig. 1.—Acute syphilitic hepatitis. Showing one of the collections of round cells (miliary gumma). This liver was much larger than normal.

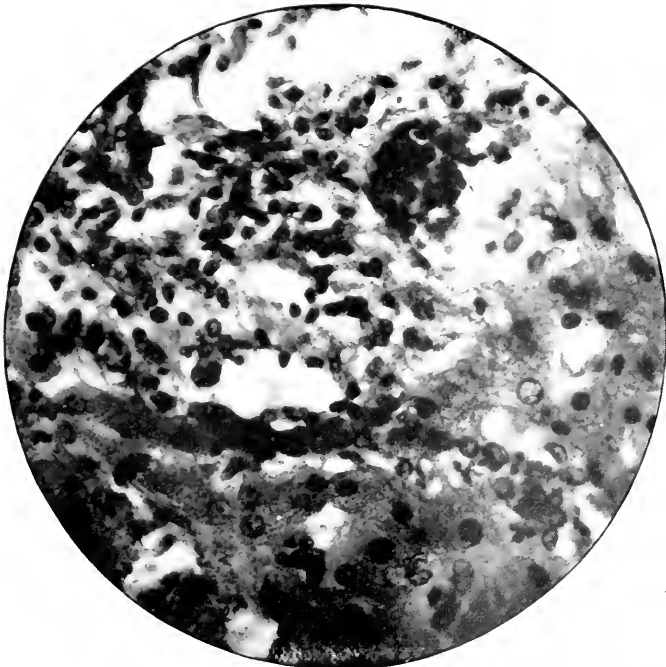


Fig. 2—Early cirrhotic changes in a syphilitic liver. (High power.) Showing numerous fibroblasts with some round cell infiltration. There is some pericellular fibrosis. This liver was greatly increased in size.



artificial lobules by these constrictions. From two or more to several dozen abnormal lobules may be thus produced. It is a rather peculiar fact that the left lobe of the liver seems to have a predilection for the formation of single large gummata. Grossly the lobulated liver usually differs from the liver of the diffuse cirrhotic type in that it is not generally uniformly enlarged. The enlargement is, instead, usually confined to one or the other lobe while the unaffected lobe may be even smaller than normal.

Microscopically the earliest stage of gummatus formation consists simply in a collection of round cells. Later a central necrotic zone forms, which becomes caseous, then cellular infiltration and fibrotic changes take place about this caseous center. Cellular infiltration may take place throughout the adjacent tissues and later the fibrosis may involve these tissues. Gummata gradually diminish in size under antisyphilitic treatment and are finally entirely replaced by fibrous tissue, unless the patient dies before resolution is complete.

The diffuse type of syphilitic cirrhosis of the liver presents a somewhat different appearance from the "hepar lobatum," just described. Upon inspection, the organ appears uniformly enlarged. The surface may show the characteristic lesions of syphilitic perihepatitis, such lesions consisting of grayish or whitish depressed scars, more or less stellate in shape although occasional linear scars may be noted. Such scars are usually rather deep, and except for them, the surface of the liver is smooth. Upon section of such syphilitic livers it is seen that the scars described may either dip down into the parenchyma of the organs, or may remain strictly localized to the capsule. Diffuse fibrotic changes are noted throughout the parenchyma, however. The whole organ is firmer than normal and cuts with resistance. As previously stated, the organ is enlarged.

Microscopically such diffusely cirrhotic livers show chiefly the perilobular type of cirrhosis, cirrhotic changes being more marked about the periphery of the individual lobules; fibrous tissue dipping freely within the lobes, however, so that usually in addition to a fibrosis of a perilobular type, both interlobular and intralobular changes may be present. In addition to such fibrotic changes active cellular infiltration about the cells may be noted (pericellular fibrosis). It is this type of syphilis of the liver to which congenital

syphilitics are said to be especially subject. Of our cases of syphilis showing cirrhotic changes in the liver, 21 out of 90 showed this type of diffuse hypertrophic cirrhosis.

*Perihepatitis.*—The pathologic findings in syphilitic perihepatitis have already been mentioned as occurring usually in connection with syphilitic cirrhosis. This condition frequently occurs alone, without cirrhosis of the liver parenchyma. Grossly, such a condition is recognized by the characteristic stellate or linear indentations in the surface of the liver of a grayish or whitish color. Such scars may vary in size from the diameter of a few millimeters to the length of several inches. Upon section of the liver through one of these scars, if the case be one of a pure perihepatitis, no involvement of the liver parenchyma will be noted, except for a slight fibrosis of tissues immediately under the scar. Syphilitic perihepatitis is very commonly found in patients dying from syphilis, being a much more common lesion than either or both of the syphilitic cirrroses described above. Microscopically, the characteristic scars are found to consist of connective tissue, with occasionally active cellular infiltration about this tissue. Rarely, minute gummata have been noted in the capsule of the liver. Adhesions may be noted between the liver and surrounding organs due to the perihepatitis, such organs as stomach, omentum, intestines and peritoneum being occasionally involved.

We have been able to find records of 25 such cases of a pure type in our series of syphilitics coming to autopsy. In these cases fibrotic changes of the parenchyma were so slight as to be overlooked or were entirely absent.

#### SYMPTOMS

*Acute Hepatitis.*—The symptoms of acute syphilitic hepatitis are characterized rather by their paucity than by their severity. In the seven cases in which I have been able to study the condition, enlargement of the liver and tenderness over that organ were the most constant findings. Jaundice was present in four cases. It was never obstructive, however, as determined by the presence of bile in the stools. In three cases the jaundice was only slight. In the fourth case it was marked. Jaundice was the chief complaint of two patients. Belching with a full, dragging sensation after eating was complained of by two patients. Pain after eating was



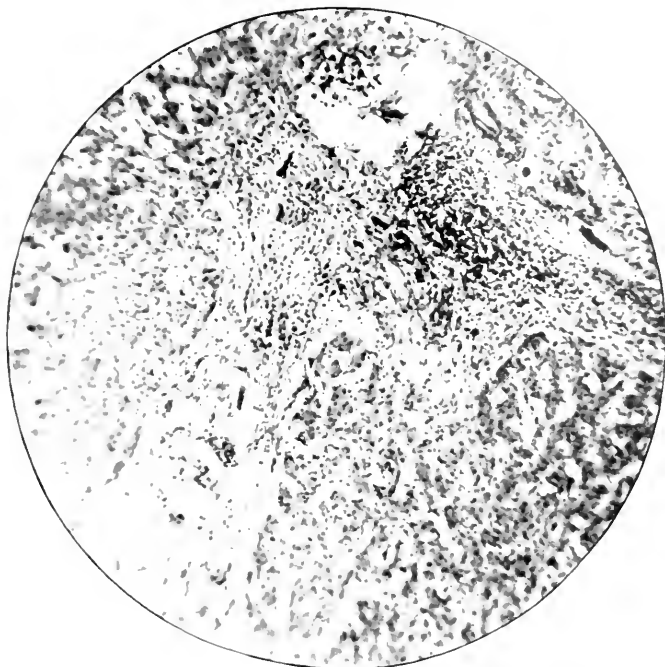


Fig. 3.—Early cirrhotic changes in a syphilitic liver. (Low power.) Showing perlobular fibrosis with occasional collections of fibroblasts and round cells. There is also some intralobular fibrosis. This liver was much larger than normal.

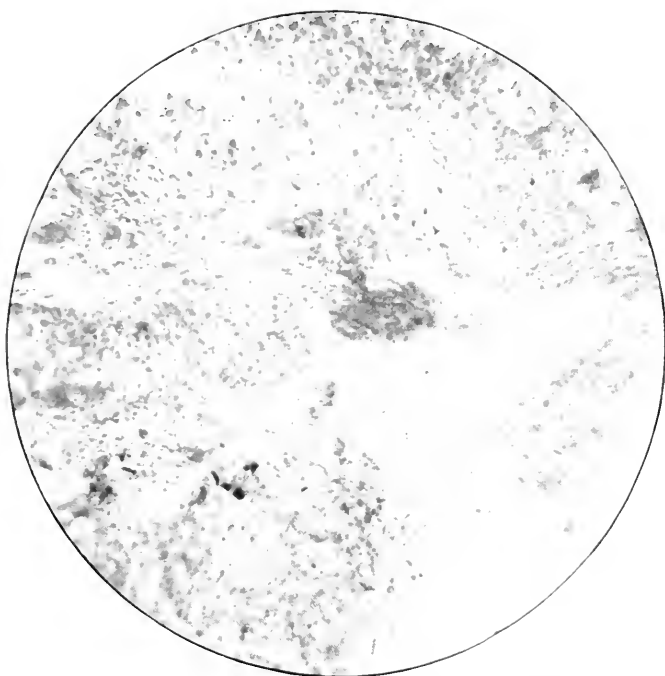


Fig. 4.—Late cirrhotic changes in a syphilitic liver. Showing diffuse perlobular and intralobular fibrosis. This liver was much smaller than normal.



complained of in one case. Pain and tenderness in the right hypochondrium was the most common of all complaints, being noted in six out of seven cases. No fever was present in four out of six cases. In two cases occasional irregular rises in temperature were noted. Enlargement of the liver varied in these cases from two fingerbreadths from the costal margin to a hand's breadth below. The surface of the liver was smooth in all cases. The enlargement was always uniform. The edge was palpable in four cases. It is interesting to note the Ewald test meals showed a complete absence of free hydrochloric acid in two of these cases, and a hypochlorhydria in one. In the remaining cases gastric analyses were not made.

In all cases prompt shrinkage of the liver with amelioration of all symptoms occurred very promptly after the initiation of the anti-syphilitic treatment. The longest period required for reduction of the liver to normal size and for coincident relief of all symptoms was two weeks, in all except one patient, who died from another cause.

*Syphilitic Cirrhosis.*—Usually the symptoms caused by the later manifestations of syphilis of the liver are much more marked than those described above. Writers on the subject almost universally agree that one of the first and most prominent of all symptoms of syphilis of the liver is pain either in the epigastrium or hypochondrium. Pain in the epigastrium may suggest the stomach as the chief offender. Tenderness over the liver is common although such tenderness is rarely so acute as that prevalent in acute inflammations of the liver and its appendages. Evidence of *dyspepsia*, fullness after meals, belching or pain after eating, etc., are common symptoms. It is not uncommon for the physician to diagnose the condition as chronic gastritis when the patient is first seen. *Loss of weight* occurs with rather unexpected rapidity in some of these cases. There is rarely much anemia, however, this fact constituting a valuable differential point between syphilis and carcinoma of the liver. The average red blood count in these cases was 4,100,000. The lowest count was 3,300,000.

*Enlargement of the liver*, either in the form of a generalized enlargement of the whole organ, or of a lobular enlargement, (enlargement of one lobe), was present in all of the thirty-four cases which were diagnosed clinically as syphilitic cirrhosis by us. *Some tenderness over the liver* was present in practically all of these cases. In a number of cases tenderness was only slight, however. *Jaundice* was

not a very common symptom in this series of late cases, being marked in only one out of thirty-four, moderate in six, and slight in three. *Ascites* was present in seven cases. *Enlargement of the spleen* was noted in six cases. *Fever* was present in a number of our cases, rarely rising above 100 degrees, however, and being usually of an intermittent or septic type, suggesting usually the fever of abscess of the liver or that of pulmonary tuberculosis. No chills were noted, except in one case. The white blood count was unchanged as a rule. The differential count was of no value in diagnosis. The average white count was 8,500; the highest count noted was 16,000. In the terminal stages of the disease death may occur with symptoms of profound intoxication, convulsions, and coma being noted as in a case seen by us.

*Syphilitic Perihepatitis*.—A friction rub over the liver, noted as a sign of syphilitic perihepatitis by others, was not present in our series of cases. Pains resembling those of pleuritis, or those of gallbladder or gastric ulcer may be present. Pains may be referred to back or shoulders. Such referred pains are rare, however.

#### PROGNOSIS

The prognosis of syphilis of the liver is good unless the disease has progressed so far as to destroy the greater part of the liver parenchyma. The average case met with in practice recovers promptly upon appropriate antisymphilitic treatment. We have treated two cases diagnosed as syphilis of the liver before death, who, in spite of treatment, went progressively from bad to worse. In both of these cases it was found at autopsy that the greater part of the liver was destroyed and replaced by gummata and fibrous tissue.

#### TREATMENT

The treatment of syphilis of the liver is similar to that used for gummata elsewhere in the body, consisting first, preferably, of potassium iodide because of its undoubted property of facilitating the absorption of gummata. This drug should be begun in ten grain doses three times daily and the amount increased daily five drops at a time up to approximately 100 to 120 minims daily if that amount is well tolerated. It is best given in the form of the saturated solution. Mercury and salvarsan or neosalvarsan should be given at appropriate intervals. It is our custom in this clinic to administer

mercury to these patients in the form of the bichloride in doses of  $\frac{1}{24}$  of a grain three times daily during the course of the iodide treatment. Intravenous injections of mercury bichloride in  $\frac{1}{10}$  grain doses every three days given after the method of Nixon have also proved successful in our hands.

Inunctions of mercury may also be used during the treatment. As soon as the liver is reduced to normal size and as soon as all symptoms caused by the disease have disappeared, potassium iodide should be interrupted in large doses, and treatment with salvarsan or neosalvarsan instituted. If neither of the arsenic preparations are available, mercury and potassium iodide should be continued over long periods of time as in the usual treatment of syphilis.

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THE CAUSES OF ARTERIAL HYPERTENSION, WITH  
SPECIAL REFERENCE TO SYPHILIS—  
A CLINICAL INQUIRY\*

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ARTERIAL hypertension, familiar as it is, presents many a puzzle. Its ultimate etiology is still an unsolved problem, and even in evident nephritis with hypertension, the exact relation of the two is scarcely beyond the field of hypothesis. Our attention is focused upon the newer chemical methods of blood examination which promise fruitful help in the solution of these problems, but at the same time the good to be derived from the clinical analysis of carefully studied hypertension cases must not be lost sight of.

I have taken a consecutive series of my private patients, six hundred and seventy-eight in number, and have selected for this study all histories which record arterial hypertension. At the outset it was difficult to fix a standard by which to govern this selection. Diastolic pressure for many reasons, offers a better measure of arterial tension than systolic pressure, and the two together in their mutual relationship are still better. The common custom, however, has been to grade hypertension according to systolic pressure and for the sake of uniformity, I have adopted such a classification. I have chosen only those patients presenting a systolic pressure of 155 mm. or more, leaving out of consideration, no doubt, a certain additional number whose blood pressure, while failing to reach this arbitrary figure, is nevertheless abnormally elevated.

Of the 678 consecutive patients there were 124 with arterial hypertension. These can be divided into the following groups:

- A. 51 patients with a systolic pressure of 155 mm. to 175 mm. inc.
- B. 43 patients with a systolic pressure of 176 mm. to 200 mm. inc.
- C. 30 patients with a systolic pressure of 200 mm. and over.

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\*Read, by invitation, before the Knox County Medical Society, Knoxville, Tenn., July 31, 1917.

Although the entire series presented the usual proportion of adults of every age, these groups of hypertension patients show a singular uniformity as to average age.

The average age of group A was 52 years.

The average age of group B was 56 years.

The average age of group C was 53 years.

The interesting studies made several years ago by Thayer upon the influence of various infections, particularly typhoid fever, in the production of arterial disease suggest that previous infection may here have an etiologic significance. Thirty-three of these patients gave a history of typhoid fever, fourteen of pneumonia, three of yellow fever and three of recent scarlet-fever. From these figures it is seen that none of these diseases, even typhoid, were present in this group with more than the usual frequency.

Alcohol does not appear to play an important role, for only six patients admitted its excessive use. It could perhaps rightly be asserted that these histories were not taken with this question particularly in view and therefore, are not dependable. The further fact, however, that forty-five per cent of these patients were females lends additional weight to the view that alcohol and tobacco were not potent factors.

It is unfortunate that the histories do not give sufficiently accurate information regarding the use of coffee, tea and coca cola, particularly as the last named beverage has come into such general use and has an immediate and at times a powerful effect upon the kidneys.

The heart was enlarged in sixty-seven instances, about fifty per cent. I was interested in finding however, that cardiac hypertrophy was noted much more uniformly in the later than in the earlier histories, a fact which can be explained by our practice of late of examining all patients in the fluoroscope or by means of tele-roentgenography. From this I would conclude that a larger proportion of these patients have demonstrably enlarged hearts than are here shown.

Nephritis unquestionably bears a definitely etiologic relation to many of these hypertension cases. Albumin alone was found in the urine in twenty-nine instances, and both albumin and casts in sixty-one, or fifty per cent of the cases. It is unfortunate that the phtha-

lein test of kidney function was made in only eleven of these, the average excretion in two hours being forty-nine per cent.

It is interesting to note that the urine of ten patients, eight per cent of the whole group, contained sugar. This is a disproportionately large incidence of glycosuria.

Some mention should be made of the blood studies in these cases. An entirely new field of clinical research has been opened by Folin, Bloor, and others in the discovery of colorimetric methods for quantitatively determining the various nitrogenous and lipoidal bodies of the blood which, because of the small amounts present have hitherto eluded clinical estimation. I hope at another time to publish in detail our blood studies, but I have already been impressed by the high value which we have almost uniformly obtained for nonprotein nitrogen, urea nitrogen, uric acid, and creatinine. Fine and Chace see unfavorable prognostic significance in creatinine values above 1 mg. to 2 mg. in 100 c.c. of blood. We are constantly finding in these patients values of 3 mg. to 5 mg., but our observation has been too brief to warrant an opinion as to the prognostic value of such estimations.

The part played by these retained bodies, as well as by cholesterol, lecithin and other substances in influencing blood pressure and arterial disease is still to be seen. It will also be interesting to determine whether these substances are uniformly present in increased amounts in essential hypertension without nephritis.

Among the focal infections were noted: four instances of diseased tonsils, four of infection of the accessory nasal cavities, forty-two of diseased teeth (35 per cent), four of chronic appendicitis, and five each of gall bladder and urinary tract infections.

At first glance, thirty-five per cent of oral sepsis is noteworthy. The entire six hundred and seventy-eight patients were examined, however, with the same attention to teeth as were those of the hypertension group, and oral sepsis was noted one hundred and seventy-one times, or in 25 per cent of all the patients. In view of these findings one would hesitate to ascribe to diseased teeth an important relationship to high blood pressure.

The part played by syphilis in the production of arterial hypertension has been variously stated. In view of my own figures it is hard to credit some of the more extravagant statements, such as that by Stoll, that fifty per cent of hypertension patients have



syphilis. The fact that Stoll based his statement upon results obtained with the luetin test may explain his figures. We are familiar with the general statement that syphilis is the chief producer of arterial disease, and we are accustomed to look upon arteriosclerosis as a cause of hypertension, but herein are two fallacies. While syphilis does produce an enormous amount of disease of the ascending aorta, of the coronary arteries and of other groups of vessels, the statement that it is the most frequent cause of widespread general arteriosclerosis may be doubted. And too, our views regarding the mutual relationship of arterial disease and hypertension are undergoing a change, for there is good reason for believing that, in many if not in most instances, the hypertension precedes rather than follows the arteriosclerosis.

In the hypertension group we found twenty-one patients, or 17.5 per cent with a positive Wassermann reaction. This test is done as a routine measure upon each of our private patients without regard to the nature of the complaint, and of the entire series of six hundred and seventy-eight patients 16.5 per cent gave a positive Wassermann reaction.

I have been deeply impressed by the predominant role played by syphilis in internal medicine, but a comparison of these figures serves to rob the disease of unusual importance in its relation to arterial hypertension.

If clinical impressions are to be trusted, one is brought to the conclusion that not one but many and widely varying factors enter into the production of arterial hypertension.

## SYPHILIS AS A CAUSE OF CHRONIC URTICARIA

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WHILE the etiology of acute urticaria is well discussed by the authors of dermatologic textbooks, that of chronic urticaria is passed over very briefly. By chronic urticaria is meant a continuous condition and not a series of acute attacks. In the literature there are but few references as to the causation of this variety of the disease, fairly common and very distressing as it is in practice. And yet there are just enough references to show that it may be due to a focal or almost concealed infection. Haase<sup>1</sup> states that in many of his cases he has found malaria and that the disease will disappear upon the proper administration of quinine. Wolff<sup>2</sup> has shown that it may occur in connection with hydatid cysts.

Four years ago a dispensary patient, a negress aged thirty-six, who had been formerly treated for late syphilis, appeared with a severe case of chronic urticaria that had lasted for almost six months. Her Wassermann proved strongly positive, and injections of mercury were at once begun, with the result that the urticaria disappeared in ten days. Negro-like she promptly stopped treatment, and in four weeks the urticaria reappeared, and again the administration of mercury stopped it promptly. Within a few weeks we had a similar experience with three other patients. We then began to make routine Wassermann examinations upon all patients with chronic urticaria, and to date have a record of eighty-nine cases with twenty-eight positive serum reactions. This is much higher than the routine positive Wassermann results in other patients, either in the wards or the clinics, where the average positive findings are about twenty per cent. We were able to follow twenty-three of the twenty-eight patients, and all were relieved of their urticaria by either mercury or salvarsan. In seven instances

<sup>1</sup>Haase: Discussion of Dr. Chipman's paper on Dermatological Dietetics, *Jour. Am. Med. Assn.*, 1916, lxxvii, 1650.

<sup>2</sup>Wolff: Mracek, *Handbuch der Hautkrankheiten*, i, 595.

we administered mercury to Wassermann-free patients suffering from chronic urticaria and in no instance was either the itching or the eruption affected.

In private practice I have tested eighteen patients who were suffering from chronic urticaria for a positive complement fixation, and in not a single instance could a positive result be obtained, hence it is probable that it is chiefly among the hospital and dispensary classes that we shall obtain the best results in chronic urticaria by searching for syphilis as a cause. At the same time this condition is such a wretched one that it behooves every practitioner to exclude syphilis in every case coming under his observation.

## THE ADVISABILITY OF PROSTATECTOMY IN THE PRESENCE OF CORD LESION\*

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IN the examination of the central nervous system of patients with urinary incontinence following prostatectomy, it is not uncommon to find definite evidence of cord lesions. On investigation it is usually discovered that the patient had complained of urinary difficulty even prior to the prostatic age and that definite evidence of a central nervous system lesion had been overlooked. The urinary symptoms were evidently the result of disturbance in the central nervous system and were not caused by the enlargement of the prostate that may have been felt per rectum. Even when no such enlargement was palpated the surgeon may have felt justified in advising a prostatectomy because of the possibility of median lobe obstruction. It is now recognized that urinary obstruction may be due to many conditions other than those discovered by means of rectal palpation and the urethral sound. When any doubt remains, the etiologic factor can usually be ascertained by a careful examination of the nervous system and by cystoscopy.

The physical examination of a series of patients who had cord lesions and who complained of urinary disturbance, showed that evidence of the lesion in the central nervous system is often apparent even on casual examination. Occasionally, however, the cord lesion is obscured and is discovered only after a careful search. Rectal examination of patients with advanced cord lesions and urinary difficulty shows that the prostate is apparently smaller than normal, the periprosthetic tissues are often flabby, and any slight degree of prostatic enlargement that may be present seems to give on pressure as though there was no resistance in the tissues back of it. Occasionally, however, the urinary difficulty seems to be caused by a well-marked enlargement of the prostate and only on careful examination is definite evidence of cord lesion determined in addition. The

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question then arises: Are we justified in performing prostatectomy in the presence of a cord lesion?

The decision as to the advisability of an operation will usually depend on the relative degree of the symptoms of obstruction due to the enlargement of the prostate and the extent of the nerve lesion. Although operation is usually contraindicated by incontinence, it may occasionally be advisable. If the incontinence is due to weakness of the external sphincter, prostatectomy is not advisable, but if the incontinence is due to overflow of retained urine, as is not infrequently the case in uncomplicated hypertrophy of the prostate, the operation may be justified. The tone and strength of the muscular coat of the bladder are best estimated by watching the change in the amount of residual urine and the force with which the stream is propelled through a catheter. If the tone is good, the urine is passed vigorously until the bladder is empty, without the use of the accessory abdominal muscles. If the muscular tone is failing, the stream flows quietly, its force being altered by any change in the abdominal muscles and by respiratory movements. It may require pressure with the hand to completely empty the bladder. Under these circumstances the organ does not contract uniformly but often falls into folds leaving separate pouches filled with urine. In such cases over-distention may temporarily increase the impairment of tone. It is said that the persistent use of a catheter sooner or later results in complete distention, and that in two years' time the expelling power will not return. This may be true when the difficulty is due to a nerve lesion. On the other hand, if the obstruction is mechanical, a catheter may be used for many years without any impairment of the expelling power and the patient will completely empty his bladder after the obstruction has been removed. The overflow, often observed in the presence of prostatic enlargement, usually begins at night when the patient is relaxed, but may be brought on by sudden exertion.

Incontinence is not a common symptom of uncomplicated prostatic enlargement. If there is true incontinence, the bladder is always found empty since the urine passes out as quickly as it enters, but if the leakage of urine is due to overflow, the bladder is always completely filled and just a small amount escapes. Incontinence may be due to the fact that the enlargement of the prostate keeps both the external and internal bladder sphincters continuously relaxed. However, we have never found a total incontinence of urine due to enlargement of the prostate. In many cases of enlargement

of the prostate, we have seen a loss of function of the internal sphincter so that the bladder and prostatic urethra were one continuous cavity, but in all instances the sphincter external to this part of the urethra was normal and did not allow the urine to escape. This shows how important it is not to disturb the external sphincter in operating for enlargement of the prostate.

True incontinence is usually due to the lesion in the nervous system. With the exception of trauma, *tabes dorsalis* is the most common form. Bladder symptoms may be the very first indication of locomotor ataxia, and as the enlargement of the gland and *tabes dorsalis* occur about the same age and time of life, it is easy to make a mistake in the diagnosis by attributing the urinary symptoms to the enlargement of the gland, when in reality, they are due to the condition of the nervous system. In only a few selected cases of co-existing enlargement of the gland and *tabes dorsalis* should operative interference be undertaken. It is easily seen that if the condition is due to a lesion of the nervous system relief will not be obtained by operating, and in all probability many patients are better off with some mechanical obstruction due to the enlarged gland than they would be with the obstruction removed and with total incontinence of urine. All tabetics do not have involvement of the portion of the cord which controls the urinary mechanism so that a person may have *tabes dorsalis* and also have good control of the bladder sphincter. Fortunately, the presence or absence of sphincter control can be demonstrated by a careful cystoscopic examination. If the cystoscopist finds that the sphincter is functioning and that the symptoms are due to the enlargement of the prostate, it is proper to remove the gland since good functional results are obtained, even though *tabes* is present. This is a very important consideration. We have frequently observed patients with a loss of sphincter control who said that under these circumstances existence was almost unbearable. When there is not a total incontinence but extreme urgency of urination, the condition is nearly as distressing because it necessitates the wearing of a urinal in order to keep the clothing dry. The functional result must be one of the chief considerations in all prostatic and bladder cases. It should be very carefully considered before any operation is attempted, especially if the patient is suffering from *tabes dorsalis*. When the clinical evidence of advanced cord lesion is well marked, there being ataxia, cerebral symptoms, or incontinence resulting from weakness of the external sphincter, operation would, of course, be contraindicated. If, however, the

cord lesion is determined only after a careful, painstaking examination it may be necessary to make a careful cystoscopic examination in order to determine the major factor in the urinary obstruction.

The data obtained by cystoscopic examination of patients suffering from lesions of the central nervous system are of much importance in the differential diagnosis. In instances in which the urinary obstruction is caused by such cord lesions, typical changes in the appearance of the interior of the bladder and the sphincters may be observed by cystoscopic and urethroscopic examination. The changes usually regarded as typical and which are most prominent are the characteristic trabeculation and relaxation of the sphincters. The trabeculae are not as coarse as is usual when there is mechanical obstruction. They appear more ridge-like and frequently extend continuously over a large part of the circumference of the bladder. Caulk and Greditzer\* maintain that the condition of the sphincters is of greater importance in the diagnosis. In a recent article, they described the relaxed condition of the internal sphincter and prostatic urethra. This atonic state of the prostatic urethra is usually accompanied by a reduction in sensation.

Young\*\* in an article in which he described a punch operation for removing median bars also says he has operated on several tabetics in this way with fairly satisfactory results.

In reviewing the surgical records of the Clinic, it was found that a prostatectomy has been done in nine patients in whom there was definite evidence of a cord lesion on clinical examination. There were also a number of patients with well marked hypertrophy of the prostate who gave a definite history of early lues. Several of these had a positive Wassermann reaction but no clinical evidence of a cord lesion and were consequently not included in this series. A study of the clinical data and a review of the postoperative results obtained is of considerable interest.

As regards the subjective symptoms other than the urinary difficulty there was an absence of definite data and more confusion than is usual in cases of cord lesions. The examination of the nervous system of most of the patients operated on showed that the upper portion of the cord was more involved than the lower. The absence of incontinence after the operation in all cases would seem to cor-

\*Caulk, J. R., and Greditzer, H. G.: Observations on the Bladder in Diseases of the Central Nervous System.—An Analytical Study of 117 Cases, *Am. Jour. Syph.*, 1917, i, 42-57.

\*\*Young, H. H.: A New Procedure (Punch Operation) for Small Prostatic Bars and Contracture of the Prostatic Orifice, *Jour. Am. Med. Assn.*, 1913, ix, 253-257.

roborate the accuracy of the preoperative examination of the nervous system. Only three patients of the nine gave a positive history of having had an initial lesion. Two gave a history of having had pain referred to the extremities, and this only to a moderate degree. A slight degree of ataxia was noted in two patients. Although in six cases the onset of symptoms had occurred more than ten years previous to our examination, in only one had it been noted before the prostatic age. The initial symptom was usually frequency of urination, difficulty becoming predominant later. The catheter was used entirely in five cases and partially in the remaining five. A slight degree of incontinence was complained of in two cases. In both of these, however, there was a large amount of residual urine and the incontinence might be explained in part as being an overflow.

Examination of the nervous system revealed the fact that the different reactions varied from the normal to a moderate degree. The patellar reflex was entirely absent in two cases and markedly exaggerated in two. The Argyll-Robertson pupil was present in four cases, a definite Rhomberg in three, and a moderate ataxia in two. The Wassermann reaction was positive in two cases and negative in five. The amount of residual urine varied from one to fourteen ounces in the five cases in which the catheter had been partially used. The functional tests (phthalein) in all cases were more than 40 per cent at the time of the operation.

On cystoscopic examination, as might be expected, the evidence of cord lesion was overshadowed by the changes resulting from mechanical urinary obstruction. The internal sphincter was relaxed in one case, but the external sphincter was not relaxed in any. As is usual in the presence of a cord lesion, cystitis was present only in a moderate degree. Stone in the bladder was a complication in one case. The degree of trabeculation was marked in only five cases, a fact suggestive of cord lesion. It would seem that when the gland is enlarged it might be difficult to determine by cystoscopic examination whether or not the urinary sphincters are relaxed. However, the knowledge of the exact degree of relaxation may not be necessary to determine the advisability of operation, since the character of the trabeculations and the appearance of the bladder wall together with the presence or absence of incontinence and the clinical findings will usually offer sufficient data.

During this same period a large number of patients were examined who had well marked clinical evidence of cord lesions, and more



or less residual urine. On cystoscopic examination they also showed definite evidence of cord lesion. Some of these patients had a moderate degree of hypertrophy of the prostate and the advisability of prostatectomy might have been considered. However, the general condition, the well advanced degree of the cord lesion as evidenced by the clinical symptoms, the dilated atonic bladder and the relaxed condition of the sphincters contraindicated operation.

In the majority of patients in advanced stages of tabes, however, even though retention is present, the prostate appears smaller than normal upon palpation per rectum, and there is an abnormal relaxation of the tissues about the prostatic area. Therefore the advisability of operation would depend largely on the comparative degree of cord involvement. When it is evident that the sphincter itself is not relaxed, that there is sufficient hypertrophy of the prostate to account for the urinary obstruction, and that the general condition is favorable, prostatectomy may be attempted.

In this connection we may refer also to the so-called atonic bladder. This condition, which has been fully described by Walker,<sup>†</sup> is characterized by a dilated bladder and residual urine without any definite evidence of disease in the nervous system or any clinical cause to account for the obstruction. Another cause for urinary obstruction is occasionally observed in cases in which the prostatic hypertrophy obstructs the urethra without causing an enlargement that can be palpated on rectal examination or observed by cystoscopic examination. Urethroscopic examination alone will reveal a peculiar overlapping of the lateral prostatic lobes which may cause marked urinary obstruction.

Answers to letters of inquiry relative to the postoperative results in these nine cases have been received from eight of the patients. One patient died eighteen months after the operation. The other eight are reported in good condition and have no urinary difficulty except in one instance. The latter was the last patient in the series to be operated on, the operation having been performed some six months ago. He still complains of considerable frequency of urination and recently of a slight degree of incontinence. The results indicate that prostatic hypertrophy was the predominant factor in the obstruction. Three of the patients underwent a thorough course of

<sup>†</sup>Walker, J. W. T.: *Atony of the Bladder Without Obstruction or Signs of Organic Nervous Diseases*, Ann. Surg., 1910, lli, 577-596.

antisyphilis treatment, including injections of salvarsan. This treatment seemed advisable, following the operation, as a preventive measure.

#### CASE REPORTS

Case 52394, a patient 72 years of age. No history of lues or previous diseases. He had had trouble for fourteen years, beginning with increased difficulty in urinating. A catheter had been used part of the time recently; some pain in the suprapubic region, perineum, and bladder. A general examination of the nervous system did not reveal a cord lesion. Cystoscopic examination showed 14 ounces of residual urine, and a typical picture of cord bladder. Cystitis (1 on a scale of 4). Trabeculations were typical of cord lesion. Suprapubic prostatectomy was performed July 28, 1911. The patient returned about a year later for the removal of stones. The use of a catheter was necessary occasionally, although the functional result was fair and apparently much benefit was derived from the operation.

Case 62477, a patient, 51 years of age, who gave a history of having had lues. He came for treatment for urinary difficulty which had started two years previously. Bladder symptoms marked; a catheter had been used continuously for three weeks, and there was considerable sacral pain. Examination of the nervous system showed that there was slight urinary incontinence. Right patellar reflex absent, left exaggerated. Pupillary reflexes slow. Rhomberg absent. One ounce of residual urine; prostate enlarged, 2; a moderate degree of cystitis. The cystoscopic picture was not wholly characteristic. Blood Wassermann test positive. A suprapubic prostatectomy was performed Jan. 10, 1912, and a good functional result was obtained. One month after the operation it became necessary to pass a sound a few times.

Case 74852, a patient 70 years of age, with a history of five years of urinary difficulty. Three years previously he had had an attack of sudden retention; he complained of pain in the back, legs, and suprapubic region. Examination of the nervous system showed an absence of patellar reflexes. Ataxia was marked. Examination of the bladder showed enlargement of the prostate, 3. The urine was all residual. There was marked typical bladder trabeculation. Suprapubic prostatectomy Oct. 14, 1912. Following the operation he had a little difficulty in urinating. He died in March, eighteen months later.

Case 82406, a patient 65 years of age. Three weeks before coming for examination he had had a severe hemorrhage from the bladder. During the past two years he had had slight hematuria and had used a catheter almost continuously for several weeks. Examination of the nervous system showed most of the characteristic symptoms of tabes. Examination of the bladder showed that all of the urine was residual; cystitis 2, stones in the bladder and marked trabeculation of the typical cord lesion type. Blood Wassermann test positive. Suprapubic prostatectomy was performed April 30, 1913. A large tabetic bladder with a thick wall and poor contracting power was found. The result in this case was very satisfactory although stones formed in the bladder and were removed elsewhere a year or more later.

Case S9916, a patient 62 years of age, who gave a history of having had lues. He came because of urinary difficulty which he had had for six months. A catheter had been used continuously for two months. He had an Argyll-Robertson pupil and Rhomberg. Cystoscopic examination showed a typical cord bladder, and in addition, considerable cystitis. The trabeculation was characteristic. Suprapubic prostatectomy April 4, 1916. At the present time this patient reports that he has gained 20 pounds and has no urinary difficulty or hematuria.

Case 107150, a patient 54 years of age, with a history of having had an injury to the spine thirty-three years previously. Since that time there had been some difficulty in urinating, though most of the trouble had come in the last three years. A catheter had been used a part of the time. Examination of the nervous system showed an absence of the patellar reflexes. Bladder examination revealed 10 ounces of residual urine. The internal bladder sphincter was relaxed and there was considerable cystitis and very marked trabeculation of the cord lesion type. Suprapubic prostatectomy June 17, 1914. A very large, thick-walled bladder was found, and after the operation there was a moderate degree of incontinence which persisted for several months. This gradually lessened and at the present time the functional result is very good, the patient reporting that he has no trouble of any kind.

Case 114446, a patient 74 years of age. He had had some sort of an injection over the bladder region fifty-three years previously. He had had his frequency for about twenty years and had used a catheter almost continuously for three years. Examination of the nervous system showed slight urinary incontinence; patellar reflexes absent; Rhomberg present; ataxia. Bladder examination showed nearly all the urine to be residual; cystitis 2, with the characteristic trabeculations and relaxation of the bladder seen in these cord cases. A suprapubic prostatectomy was performed Sept. 24, 1914, with a good result except that the frequency persists and urination occurs every few hours.

Case 177201, a patient 68 years of age, who had had urinary frequency for fifteen years and had used a catheter off and on for two years. He complained of some pain in the legs. Examination of the nervous system showed that the patellar reflexes were diminished and the pupils responded slowly; Rhomberg present. A bladder examination showed 6 ounces of residual urine; cystitis 2. A suprapubic prostatectomy, performed Nov. 21, 1916, had a satisfactory result as far as function is concerned but the cystitis has persisted, and occasionally there is some difficulty of urination and the passage of a little blood.

Case 178746, a patient 67 years of age, with a history of having had lues. He came because of difficulty of urination which began ten years before. He had used a catheter off and on for nine months. On examining his nervous system it was found that the pupillary reflexes were unequal and sluggish. Rhomberg was present. Bladder examination showed 8 ounces of residual urine with cystitis and typical trabeculations. A suprapubic prostatectomy was performed Dec. 20, 1916, and was an entire success. The patient still complains of feeling awkward below the knees.

## THE ROENTGEN DIAGNOSIS OF LUNG SYPHILIS

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LUNG syphilis, the pathology of which was described by Virchow, has not yet received serious attention at the hands of medical writers. The bibliography appended hereto lists the chief articles of recent years on this subject. In these, there are only cursory references to the roentgen shadows of this condition.

Moore and Carman<sup>1</sup> mention it in a paper on metastatic lung cancer, quoting Rothschild to the effect that syphilis of the lung casts a diffuse shadow. Abner Post<sup>2</sup> has described two cases of lung syphilis and demonstrated their roentgen shadows. Lieut. Calender<sup>3</sup> makes the following statement in a paper on Pulmonary Tuberculosis: "Pulmonary syphilis gives a picture quite distinct from that of phthisis; the shadows are clear cut and sharp, with no tendency to mossiness of the borders and the disease can be readily diagnosed by the roentgenogram." Solomon Bauch<sup>4</sup> reports two cases of lung syphilis and describes the roentgen findings. Dunham<sup>5</sup> mentions syphilis of the lung but infers that it does not cast a characteristic shadow. With the exception of these passing references, the subject has been given scant attention by roentgenologists.

The belief that lung syphilis is rare is based on a misconception; namely, that it always occurs as a large gumma or as small multiple gummata. Virchow taught that the disease occurs as an interstitial pulmonitis, and if we will hold this fundamental pathologic fact in mind, we will find that the disease is far more frequent than we have supposed. Stanley<sup>6</sup> describes three forms of lung syphilis and roentgenographic shadows will be found to correspond to this classification.

1. *Syphilitic Consolidation*.—This is an acute interstitial pneumonia, in which there is an intense cell proliferation, filling the alveoli, infiltrating the septa, peribronchial, subpleural and perivascular tissues. On the roentgenogram, this presents a massive



Fig. 1.—Showing neoplasm of lung with distinct margin.



Fig. 2.—Unresolved pneumonia, resembling lung syphilis.



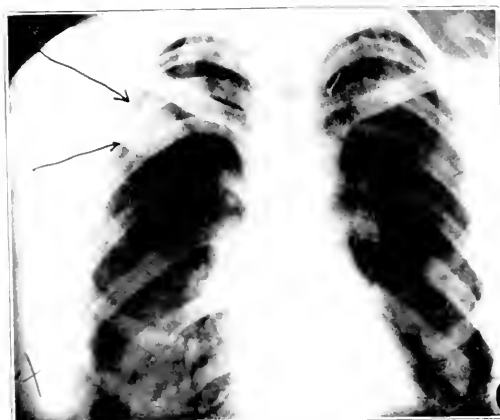


Fig. 3.—Typical peribular shadow of tuberculosis.



Fig. 4.—Syphilitic consolidation resembling pneumonia.





shadow, involving either an entire lobe, or a large portion of a lobe contiguous to the mediastinum, diminishing in density toward the periphery.

2. *Early Diffuse Sclerosis*.—In this form small miliary gummata are sometimes found. Usually the characteristic roentgenogram represents an evenly distributed, radiating, linear marking, or a diffuse speckling, throughout the lung, sometimes bilateral.

3. *Dense Sclerosis*.—Through the deposit of elastic tissue, the lung is contracted and misshapen and the pleura is thickened. The roentgenogram of this type has a characteristic pyramidal-shaped shadow, with the base at the hilum, and with lancee-like projections into the lung substance. This shadow is to be looked for in the lower or middle lobe, and not in the apex or upper lobe, as in tuberculosis.

Roentgenographically, lung syphilis needs to be distinguished from bronchiectasis, abscess, malignant tumors, pneumonokoniosis, unresolved pneumonia, and tuberculosis.

Neither the shadows of bronchiectasis nor those of abscess should be mistaken for syphilis, since, in them, the cavity is a characteristic, whereas in syphilis absence of cavity is a peculiarity.

Cancer (Fig. 1) may give a shadow with a sharp margin, in which case there is no excuse for confusing them, because the shadow of syphilis has a very irregular border (contrary to Callender's statement). Infiltrating carcinoma can not be differentiated from syphilis by its shadow, the diagnosis depending on accompanying symptoms and serologic methods.

Pneumonokoniosis presents difficulty, the shadow resembling the appearance of combined syphilis and tuberculosis. The probabilities are that any pneumonokoniotic patient, with a positive Wassermann, will have some foci of syphilis in the lungs.

Unresolved pneumonia (Fig. 2) can not be differentiated from syphilitic consolidation by its roentgen shadow; however, with the diagnosis narrowed to these two conditions, the clinical history and laboratory methods will clear the diagnosis.

Differentiation between syphilis and tuberculosis of the lungs is not always easy, but there are distinctive shadows which may be sought for and can usually be found. Dr. Wm. Snow Miller<sup>7</sup> says: "For the correct interpretation of roentgenograms of the lungs, definite knowledge of the distribution of the bronchi, the arteries,

the veins, the lymphoid tissue, the lymph follicles and lymph nodes within the normal lung, is necessary, for it is impossible correctly to understand the pathologic without a previous knowledge of the normal." Not only is this true, but in order to appreciate the difference between the shadows of syphilis and those of tuberculosis, it is necessary to have clearly in mind the essential pathology of the two infections and their pathways of invasion into the lung.

According to Fordyce<sup>8</sup> all syphilitic lesions, except the chancre and macule, are perivascular. The essential pathology, in all stages and in all tissues, is a perivascular infiltration of lymphoid cells, spreading along the vascular stems like a sleeve, or following the arteries as an endo- or meso-arteritis. On the other hand, tuberculosis is a lymphocytic cell infiltration which spreads along the lymph channels and proliferates in collections of lymph cells.

If, now, we will recall the architecture of the pulmonary lobule, which is the lung unit and the basis on which we must formulate an understanding of pulmonary shadows, we will see how beautifully it is adapted to the formation of distinctive shadows in these two diseases. Our knowledge of the anatomy of the pulmonary lobule is due to the beautiful work of Miller, of the University of Wisconsin, whose illustrations are familiar to us. The pulmonary lobule consists of the ramifications and air sacs of a terminal bronchus, corresponding in distribution to a terminal artery. The smaller bronchi and bronchioles within the lobule are accompanied by branches of the pulmonary and bronchial arteries, *but not by veins*. There are no veins within the lobule, except the small venules which arise one from the tip of each ductus alveolaris and pass immediately to the periphery of the lobule. Also the *main lymphatic trunks are extra-lobular*, following the courses of the veins. At the entrance to each lobule, the vein lies in fairly close proximity to the bronchus, but from this point it diverges and encircles the outer boundary of the lobule. At practically every venous bifurcation, there is a collection of lymphoid cells into which the lymph capillaries enmeshing the lobule drain. These collections of cells are analogous to the bronchial glands nearer the hilum.

When the tuberculous infection leaves the tracheo-bronchial glands at the hilum, there is a very consistent tendency for it to pass through intervening glands and main lymph channels, in order



Fig. 5.—Syphilitic consolidation, involving portion of lobe. Note the irregular edge and pointed projections.



Fig. 6.—Diffuse sclerosis, due to syphilis.





Fig. 7.—Diffuse sclerosis with aneurysm.

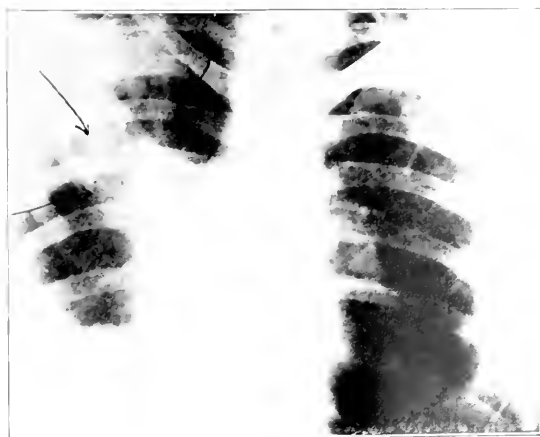


Fig. 8.—Dense sclerosis, due to syphilis.



to localize and proliferate in the lymph tissues which enmesh the lobules lying directly beneath the pleura, outlining these with the familiar triangular shadows described by Dunham.<sup>5</sup> Or, if we accept the conclusions of Ghon, and consider the lobular infection to be the primary focus and the infection at the hilum secondary, the characteristics of the shadows would be the same. The characteristic of tuberculous infection, as shown by its roentgen shadow, is that it is perilobular (Fig. 3).

A syphilitic infection spreading along the arterial stems, invades the interior of the lobule, the cellular deposits and resulting sclerosis giving a dense, irregular shadow. The differential characteristics of the two shadows are as follows:

#### TUBERCULOSIS

Tends to invade the upper lobes.

Characteristic shadows are found surrounding the apical or subpleural lobules.

The shadows are perilobular and show a definite relation to some branch of the bronchial tree.

#### SYPHILIS

Tends to invade the lower and middle lobes (contrary to Landis' statement).

Tends to involve the tissue at the hilum first, so that the densest shadow is there, diminishing toward the periphery.

The shadows do not bear a distinct relation to the bronchi and, at their edges, have either a ragged, worm-eaten appearance; or the lung is evenly speckled; or there are lance-like radiations of dense elastic tissue.

The most striking differential characteristic in the patient is the difference in the general appearance. Tuberculous patients will usually show some physical evidence of undermined health, loss of weight, anemia, etc., whereas patients with lung syphilis always look surprisingly healthy, preserving their weight and having a plethoric rather than an anemic appearance. This difference does not, of course, hold when the patient has both infections.

The following five cases have been chosen to demonstrate the typical roentgen markings of lung syphilis. In three of them the suggestion of syphilis was FIRST made by the roentgenogram, subsequently confirmed by serologic examination and clinical course of the disease. Other examples from a series of about twenty-five proven cases of lung syphilis could be shown, but space will not permit.

Case I (Fig. 4). Referred by Dr. E. P. Palmer. This case, a robust man of excellent physique had, for two years, been coughing and expectorating mucopurulent sputum. Was given roentgenographic examination which showed what appeared to be an unresolved pneumonia. The lack of clinical history led to the suggestion of specific origin. Wassermann being positive, antiluetic treatment was given, under which the lesion disappeared.

Case II (Fig. 5). Referred by Dr. R. E. Thomas. This patient, suffering from heart decompensation, gave a positive Wassermann, and one week later was examined by the x-ray, showing dense area of partial consolidation in one lung, with syphilitic heart. Subsequent examination, after vigorous treatment, showed marked change in the lung, with almost complete disappearance of the shadow.

Case III (Fig. 6). Referred by Dr. F. H. Redewill. This patient was sent for examination on account of dyspnea. The dilated heart explained the dyspnea, but the diffuse sclerosis through the lung was almost conclusive of syphilis. This was subsequently established by positive Wassermann and subsidence of symptoms under treatment.

Case IV (Fig. 7). Referred by Dr. Orville H. Brown. This patient, sent for routine chest roentgenogram before physical examination was made, was returned with the report that he had syphilitic involvement of heart and lung. The diffuse sclerosis is just as characteristic as the aneurysm. A positive Wassermann further confirmed the diagnosis.

Case V (Figs. 8 and 9). Patient of Dr. Willard Smith. Radiograph made in April, 1913, and interpreted as tuberculosis, although the patient was a known luetic. Four years later, after establishing the markings of syphilis in the lung, and knowing that this patient had been adequately treated, she was reexamined. The former dense sclerosis was seen to have completely disappeared (Fig. 9). This is a typical illustration of syphilitic dense sclerosis.

Space is afforded to consider, only very briefly, a very important division of this subject; namely, tuberculosis and syphilis as a symbiotic infection in the lung. During residence work at a sanatorium for tuberculosis, in 1912, attention was directed to Dr. Carl Spengler's "Arbeit" on these combined infections, and observations have been continued since that time. Dr. Spengler introduces<sup>9</sup> one of his papers with this statement:

"A study of years into the frequency and importance of the share of hereditary and acquired lues as the foundation for and its effect upon, the development of tuberculosis has shown that, especially the hereditary lues, in an extraordinarily large percentage of phthisics, plays a role which is highly important."

Recent papers by Potter,<sup>10</sup> Landis and Lewis,<sup>11</sup> Babcock,<sup>12</sup> and others, confirm this observation. Babcock thinks that a lues ac-





Fig. 9.—Same as Fig. 8, after resolution.



Fig. 10.—Tuberculosis and syphilis.



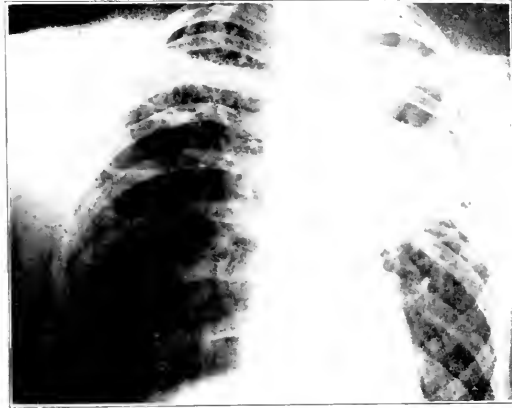


Fig. 11.—Tuberculosis and syphilis.



Fig. 12.—Tuberculosis and syphilis.



quired in the early stages of the development of tuberculosis may, through the increased tendency to fibrosis, help to arrest the tuberculous process. But, on the other hand, if tuberculosis invades a lung already weakened by syphilis, the progress of the tuberculosis will be unusually rapid. In our observations, it has been partly on the unexpectedly rapid invasion and widespread distribution of the shadows in the face of a disproportionately good physical condition, and partly on the character of the shadows themselves, that a suspicion of double infection has been based.

Three plates have been chosen from over one hundred showing the characteristics of this double infection, to illustrate the features mentioned.

Fig. 10 is a radiograph of an elderly man who suddenly developed an acute tuberculous infection of both lungs. Roentgenogram suggested the preexistence of some other infection. The aortic dilatation, with a positive Wassermann and partial disappearance of the shadows under salvarsan justified the diagnosis. Patient died from the tuberculosis.

Fig. 11. The pyramidal shadow with base at the hilum calls for some other explanation than tuberculosis. Although giving a negative Wassermann, patient was placed on specific treatment, under which he is improving.

Fig. 12. The significant thing in this patient was the apparently good physical condition, good blood condition, and widely distributed lung shadows. The excellent habit of a routine Wassermann on all tuberculous patients, as practiced by his physician, showed this case to be a combined infection.

Observations on approximately one thousand chest roentgenograms justify the assertion that not fewer than fifteen per cent of tuberculous patients will be found to have this symbiotic infection.

It is hoped that this preliminary report will stimulate investigation in a field which, obviously, is a very important one and one which has not received the attention it deserves.

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## A PROPOSED STANDARDIZATION OF THE WASSERMANN REACTION

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THERE still is considerable dissatisfaction with the Wassermann reaction. To some extent this may be due to the natural tendency to expect too much of laboratory diagnostic tests; but is largely the result of weaknesses in the reaction itself or in the way it is performed. A good deal has been written on the subject of the paradoxical Wassermann reaction, a weak positive serum divided among several laboratories being reported as positive by one, doubtful by a second, and negative by a third, all reliable workers. Such apparent contradictions are due to unavoidable fluctuations in the strength of the reaction which occur in spite of the greatest care in technic. These fluctuations are explained by the fact that antigens vary in their combining power with different sera, and that complement is titrated for its value in the hemolytic system only, instead of for its power of being bound in the syphilitic system.

The greatest fault to be found with the Wassermann test, and the one for which the serologist can offer no excuse, is the false positive reaction, which occurs entirely too often and not seldom plays havoc with the lives of innocent victims. It is due either to errors in technic or to errors in judgment in reading and reporting results. The technical errors are guarded against by the controls with serum alone, with antigen alone, and with a known negative serum. Only the control with a known positive serum remains to be marshalled against the danger of drawing the reaction too fine, and this I propose to do. The errors of judgment responsible for false positive reactions are more difficult to dispose of. As a means to this end, the formulation of definite rules as to what should or should not be reported as a positive reaction is desirable. This leads to the neces-

sity of a standardization of the Wassermann reaction, long desired, but difficult to attain. So many are the slight variations in the technic even of those who perform the real Wassermann reaction, that hardly two serologists can be found who agree on the best methods throughout the test. The New York committee appointed in 1915 by Dr. Emerson to consider this subject, found it impracticable to attempt to reconcile the different methods or to prescribe a standard technic. A standard is required which is adaptable to any technic, which will show exactly when the reaction is at its point of highest efficiency, when it is too weak, allowing weak positive sera to escape detection, and when too strong, overstepping the limit of safety, beyond which lies the false positive reaction.

Titration of the strength of positive sera, proposed by Boas in 1909<sup>1</sup> is a valuable index of the amount of reagin in syphilitic sera. It can be used only with difficulty for delicate comparisons between the specimens of serum drawn at intervals during the treatment of a case because of the variation in the strength of reaction, which may, without change in the amount of reagin, cause a stronger or weaker titration of the second specimen, giving a false increase or decrease of strength. To avoid such error, it is necessary to preserve the first specimen of serum for titration in the same set of tests with the second specimen, thus insuring the same conditions. In a recent series of such comparisons,<sup>2</sup> I found the method of preservation by freezing very tedious, and welcomed the suggestion of Reudiger<sup>3</sup> to dilute the serum with an equal quantity of glycerin. This method has been very satisfactory, with the observation of certain precautions. As Reudiger warns, and I can substantiate, glycerinized sera tend to become anticomplementary. In the preservation of negative or weak positive sera, tested in the full dose, 0.2 c.c., this is of importance; but in the case of very strong positive sera, giving full deviation of complement with a very small amount of serum, the anticomplementary action of the glycerin is negligible. Strong positive sera thus preserved for over four months have not changed in strength. Most of them have been kept in the refrigerator, but several specimens exposed to summer temperature for over a month have shown no change. No attempt has been made to sterilize the glycerin, nor to protect the glycerinized serum from contamination beyond the observation of ordinary cleanliness. Owing to the difficulty of measuring glycerin accurately, the glycerinized



serum has been titrated parallel to the fresh serum, and any variation recorded for the correction of future tests.

Titration of serum has not found favor with many serologists because of its variability, due to its sensitiveness to variations in the strength of the reaction. This sensitiveness makes it a very delicate index of such variations, affording accurate means of comparing tests made at different times or in different laboratories. A mixture of several very strong positive sera preserved with glycerin is titrated with the full dose of a certain antigen each time the Wassermann reaction is made. A few trials will show the titer of this mixture when the reaction is at its point of highest efficiency. The mixture of glycerinized sera can then be titrated as the positive serum control with each set of tests, showing exactly the strength of the reaction, whether stronger or weaker than it should be. If much weaker, sera giving negative reactions should be retested. If stronger, the danger of false positive reactions will be recognized. For instance, the control serum titrates, at the point of maximum efficiency, 0.01 c.c., that is, 0.01 c.c. is the smallest amount causing complete deviation of complement. If a set of tests results in a titer of 0.005 c.c. for the control, all weak positive sera are retested before being reported. If on another occasion, the titer of the control serum rises to 0.02 or 0.05 c.c., sera giving negative results in this set of tests are retested.

This method of standardization necessitates, of course, standardized antigens. Such a possibility was suggested long ago in the fact, brought out by Boas,<sup>4</sup> that the serum of most cases of early, untreated secondary syphilis titrates with good antigens, 0.01 to 0.05 c.c. Such a standard has been maintained by me<sup>5</sup> for several years, and to require of all serologists that their antigens measure up to it would be no great hardship. Where the serum from one guinea pig is used as complement, considerable variation in the strength of good antigens must occasionally be expected, but they should not be rejected on this account, and this difficulty can be overcome by the use of a mixture of sera as complement. Ottenberg, in a recent article of great value<sup>6</sup> suggests that the maximum efficiency of antigen is not always found at the maximum safe dose of that antigen, and offers titration of positive serum as a means of discovering the dilution of maximum efficiency. The mixture of positive sera suggested as a control affords an excellent medium of

comparison between antigens. It must not be inferred, however, that this method of standardization is offered as a substitute for the old method of judging the efficiency of an antigen by trial with a series of known negative and known positive sera. It is suggested as an added test of efficiency. Antigens titrating about evenly with the standard control may vary widely in strength with weak positive sera, one reacting much stronger than the other with one such serum, only to give a weaker reaction with another. This difficulty must be met by the use of several antigens for each test, as has been the custom in the past.

The mixture of glycerinized positive sera may be valuable not only as an added protection to the serologist using it as his positive serum control, but, if as satisfactory in other hands as in mine, might easily be used for standardization of the reaction in the various laboratories. A central depot, under government control, perhaps, could make up and standardize such a mixture of strong positive sera in large quantities, giving it out in small amounts to the various serologists to use in standardizing their own positive control mixtures. Before one such standard control is used up, another supply can be made up and standardized by parallel titration.

The difficulty of holding the Wassermann reaction at the point of maximum efficiency has always been one of the tests of the judgment of the serologist. Titration of complement, no matter how carefully done, does not give entire satisfaction, and several more complicated methods of titration have been suggested to determine other factors, such as the anticomplementary titer of antigen alone, or of antigen and pooled negative sera. None of them seems to give complete satisfaction, probably, as Ottenberg<sup>6</sup> points out, because they determine other values than the combining power of complement in the syphilitic system itself. An attempt to obtain such a value by titrating complement against the combination of antigen and the titer of the standard control mixture has given interesting but not wholly satisfactory results. The titer thus obtained has varied with different antigens and has been sometimes so near the hemolytic titer that dependence upon it was considered unwise. Further experience is necessary before the method can be recommended.

The objection may be raised that in the proposed method of standardization everything is made to depend on the constancy of strength of the mixture of glycerinized positive sera. This is granted. Only

in case such controls remain constant in strength for several months can they be useful. It is easy to watch for variation in strength by titrations of serum from early syphilis and by the behavior of known negative sera.

All quantities in this article refer to the 5.0 c.c. Wassermann reaction, in accordance with my own practice and the suggestion of Ottenberg<sup>6</sup> that all quantitative reports on the Wassermann reaction should be reduced to the 5.0 c.c. standard to facilitate comparison of methods. Quantitative references to glycerinized serum take no account of the glycerin, but only the actual amount of serum.

#### SUMMARY

1. Standardization of the Wassermann reaction is desirable to increase safety and efficiency in this important diagnostic aid.

2. A practical standard must be adaptable to many slight differences in technique.

3. A mixture of strong positive sera preserved with glycerin, to be titrated with each set of tests, affords such a standard.

4. Antigens must be standardized by the titration of positive sera.

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## WASSERMANN REACTION IN FOUR HUNDRED CASES INVESTIGATED BY GROUP STUDY METHODS\*

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THE material in this paper is based on a review of the records of four hundred cases studied routinely by the Diagnostic Section of St. Luke's Hospital, San Francisco. Nearly all of these patients belonged to the middle classes and were, for the most part, chronically ill. The purpose of this study is to collect the findings in those cases which gave evidence of syphilis, and especially those findings which relate to the following points: 1. The relative prevalence of the disease in male and female in this series. 2. The gross types of the disease present. 3. The relative value of the history, Wassermann, and clinical examinations. Regarding the degree of care and completeness with which these records were compiled, the following details are explanatory: Each case was under observation in the hospital on an average of 4.8 days. By the end of this time, all the clinical procedures were completed and recorded. The study of each case consisted of a history, physical examinations in eleven departments of medicine, and laboratory examinations, including the Wassermann, in all but six. Four charts have been compiled to assist in the presentation of the findings of these examinations.

In the study of Chart I, it is shown that there were forty-six more females than males but the males were approximately five times more frequently syphilitic. The diagnosis of syphilis has been gathered together on the chart in five divisions: General syphilis, cerebrospinal, general paresis of the insane, vascular, and bones. Adding the cerebrospinal and the general paresis of the insane cases, we have twenty-five out of the fifty-one, approximately fifty per cent of the cases, neurologic. It is interesting to observe that in the twenty-five cerebrospinal cases, only three were women. It is matter of speculation why so many more women present themselves

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\*Read before San Francisco County Medical Society, September 4th, 1917.

CHART I  
400 CASES

MALE..... 177 ..... 41, or 23 %, SYPHILITIC  
FEMALE.... 223 ..... 10, or 4.4%, SYPHILITIC

DIAGNOSIS OF SYPHILIS	MALES		FEMALES		TOTAL	
	No.	%	No.	%	No.	%
General	15	8.5	6	2.7	21	5.2
Cerebrospinal	17	9.6	3	1.3	20	5.0
G. P. I.	5	2.8	0	0.0	5	1.2
Vascular	3	1.7	1	0.4	4	1.0
Bones	1	1.	0	0.0	1	0.2
Total	41	23.0	10.0	4.0	51	12.6

for chronic illnesses and why syphilis in men so predominates; and still more so why such a large percentage of chronic syphilitics give evidence of nervous system involvement, and why in this group so few of the women belong to the cerebrospinal division.

CHART II  
51 POSITIVE DIAGNOSES

HISTORY	WASSERMANN	PHYSICAL EXAM.	DIAGNOSIS			
-	+	+	13			
+	+	+	11			
-	+	?	5			
+	-	+	4			
?	+	+	4			
-	-	?	3			
-	-	+	2			
?	?	?	2			
+	+	-	2			
-	?	?	2			
-	+	-	1			
-	?	+	1			
?	-	+	1			
No.	%	No.	%	No.	%	
+	17	33.4	36	70.6	36	70.6
?	7	13.7	5	9.8	12	23.5
-	27	52.9	10	19.6	3	5.9
51	100.0	51	100.0	51	100.0	

Chart II summarizes the findings in each case in respect to the history, Wassermann, and physical examinations. All the physical findings are grouped in one vertical column so that it represents the eleven departments lined up against the history and Wassermann.

The signs +, ? and - are used to show whether the findings in each instance are positive, questionable, or negative for syphilis. For instance, a history of chancre was considered a positive history. By this method of charting, the relative value of different departments and all combinations, as well, can be made graphic and summarized at a glance. This chart shows the history positive in 33.4 per cent, doubtful in 13.7 per cent, and negative in about 53 per cent. The Wassermann gave, on the other hand, positive results in 70.6 per cent. In approximately 10 per cent, it was questionable, while in nearly 20 per cent the Wassermann gave no evidence of syphilis. It is instructive to observe that the column of physical examinations gives positive evidence for syphilis in the same percentage of cases as the Wassermann, namely, 70.6 per cent, while there were only 6 per cent of the physical examinations that were negative against the 20 per cent of negative Wassermans. From this evidence, it is concluded that more than half of the syphilitic patients gave a negative history; that in 20 per cent of the cases, the Wassermann reaction is misleading, and that the greatest aid in ascertaining the condition of the patient, as far as syphilis is concerned, is the physical examination.

CHART III  
17 QUESTIONABLE DIAGNOSES

	NO.	%	NO.	%	NO.	%
+	1	5.8	1	5.8	3	17.6
?	3	17.6	5	29.5	13	76.5
-	13	76.4	11	64.7	1	5.9
	17	100.0	17	100.0	17	100.0

Chart III presents seventeen cases that were questionable syphilities. In this group, approximately 76 per cent gave an absolutely negative history. Approximately 65 per cent gave negative Wassermans and 6 per cent gave negative physical examinations. The physical examination is suggestive many times of syphilis when it can not be proved.

Chart IV presents the negative syphilitic cases. In this division, one-half of one per cent gave a history that seemed to be syphilitic, one per cent positive Wassermann reaction and one-quarter of one per cent gave a physical examination which could be put down as evidence of syphilis; yet the evidence of history, Wassermann, and

CHART IV  
332 NEGATIVE DIAGNOSES

HISTORY			WASSERMANN		PHYSICAL EXAM.	
	NO.	%	NO.	%	NO.	%
+	2	.6	4	1.2	1	.4
?	7	2.2	3	.9	10	3.0
-	323	97.2	319	96.1	321	96.6
0			6	1.8		
	332	100.0	332.0	100.0	332	

physical examination was such that a negative diagnosis was the only conclusion justifiable.

The summary, then, of the four hundred cases studied is: That men are five times more frequently syphilitic than women; that the central nervous system leaves demonstrable traces of the disease in 50 per cent of the cases; that most of the cerebrospinal syphilis cases are in the male division; that the most important single method of examination for syphilis is the physical examination, the Wassermann second and the history least. The most convincing clinical diagnosis is when physical examination, Wassermann and history are all positive, the next in importance where two are positive and one negative, and the least where but one gives positive evidence.

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# A MODIFIED WASSERMANN TECHNIC BASED UPON THE RAPID FIXATION OF COMPLEMENT PRESENT IN HUMAN SERUM

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THE use of a complement-fixation test for syphilis in which the natural complement and the antishoop amboceptor in the patient's own serum are employed has become fairly common in controlling the Wassermann test. Probably the best known method based upon this principle is that introduced by Hecht<sup>1</sup> which was modified by Weinberg and still later further modified by Gradwohl.<sup>2</sup> This Hecht-Weinberg-Gradwohl method will, for the sake of brevity, be referred to as the Gradwohl method. After employing this Gradwohl method in a series of cases, a further modification was made by us by which it became evident that the natural complement of human blood serum combines with great readiness with the syphilitic antibody in the presence of lipoidal antigens. This union occurs much more readily than does that between the same complement and the antishoop amboceptor of the patient's serum in the presence of sheep corpuscles. In fact, this is so marked that if the proper quantity of the patient's serum is employed, the sheep corpuscles may be added to the tubes at the same time that the lipoidal antigen is added and then incubated without any previous period of complement fixation. The results are so constant that it appears that this technic may be employed to advantage to control the routine Wassermann test. As the patient's serum in this method is necessarily used without inactivating, there is no decrease of the syphilitic antibody as probably occurs in heating serum to 55° C. for 30 minutes; also as the serum is not incubated at 37° C. before the sheep corpuscles are added, there is no destruction of complement and only a minimum amount of serum need be used for the test. We have now employed this method in a series of 900 cases,

<sup>1</sup>Hecht, Hugo: *Wien. klin. Wchnschr.*, 1909, xxii, 338.

<sup>2</sup>Gradwohl, R. B. H.: *Jour. Am. Med. Assn.*, 1914, lxiii, 240; *Ibid.*, 1917, lxviii, 514.



paralleled by the routine Wassermann test, with satisfactory results.

It is desirable to describe briefly the technic of the Gradwohl method before giving that employed by us. As already indicated, the complement and the antish sheep amboceptor of the patient's own serum are utilized in this test. Accordingly in using it there is first determined the amount of 5 per cent suspension of sheep corpuscles which is completely hemolyzed by .1 c.c. of the patient's serum and this amount is taken as the "hemolytic index" of that particular serum. From this index is then estimated the amount of the corpuscle suspension to be used in making the test. In most cases this represents only a fraction of the total amount of corpuscle suspension which .1 c.c. of the serum can hemolyze; for example, if this quantity of serum can hemolyze .1 c.c. of the 5 per cent suspension of sheep corpuscles, as found in determining the hemolytic index, only one-fifth of this amount or .2 c.c. is employed in carrying out the test. In making the test itself four tubes are used, the last one serving as a serum control and not receiving any antigen, while the other three receive increasing amounts of antigen. Each tube also receives .1 c.c. of the patient's serum and a sufficient saline solution to equalize the volume in each. They are kept in the water-bath at 37° C. for thirty minutes, after which the sheep corpuscle suspension in the amount computed from the hemolytic index is added to each tube and they are kept in the water-bath for thirty minutes longer. The reading is then made.

We have tried this method of Gradwohl in 250 cases controlled by the routine Wassermann test and also paralleled by the method about to be described, and it has not proved entirely satisfactory. In 14 per cent of the cases no hemolytic index could be obtained. In about 64 per cent, where an index was obtained, it was so low that according to Gradwohl's own statement, the results of the reaction must be regarded as of doubtful value. In this 64 per cent, and in the remaining 22 per cent where the index was higher, the results did not agree well enough with those of the routine Wassermann test to make the method appear to be of great value. Nor did it prove more sensitive than the regular Wassermann test. On the contrary, it gave a smaller number of positive tests. This appears to be due to the discrepancy between the amount of sheep corpuscles used for the test and the entire amount which the same quantity of serum used can hemolyze as shown in the hemolytic index; in other

words, due to the use of an excessive quantity of either complement or amboceptor or both. However it is only fair to state that the only antigen used by us in making these tests by the Gradwohl method was an alcoholic extract of human heart, half saturated with cholesterin.

The technic of the Gradwohl test for determining the hemolytic index was then modified by us by using a definite quantity of sheep corpuscle suspension in each tube and finding the smallest amount of the patient's serum which would produce complete hemolysis in 30 minutes in the water-bath at 37° C. The amount of sheep corpuscles determined upon was the same as that employed in our routine Wassermann test, .1 c.c. of a 5 per cent suspension in each tube, the entire quantity of material in the tube eventually being made up to .5 c.c. The technic is shown in Table I.

TABLE I  
FINDING THE HEMOLYTIC INDEX IN THE MODIFIED METHOD DESCRIBED

Tubes	1	2	3	4	5	6	7	8	9	10
Unheated serum	.01	.02	.03	.04	.05	.06	.07	.08	.09	.10
.5% sheep corpuscles	.1 c.c. in each tube.									
.85% salt solution	up to .5 c.c.									

Incubate in the water-bath for 30 minutes at 37° C. Shake occasionally. Read index.

The tube containing the smallest amount of serum which shows complete hemolysis is taken as indicating the hemolytic index. Thus, if Tube 5 is the one in which hemolysis is complete, the index is 5, indicating that .05 c.c. of that particular serum is sufficient to hemolyze .1 c.c. of 5 per cent suspension of sheep corpuscles. In about one-sixth of the sera in this series no hemolytic index was secured by this first test. In such cases a second series is set up similar to the above but having .11 c.c. of serum in the first tube and .01 more in each succeeding tube. In this series, if Tube 5 is the lowest one to show hemolysis, the hemolytic index is 15; that is, .15 c.c. of the serum is required for hemolysis. Over 80 per cent of the sera in this series, 731 out of 900, gave hemolytic indices between 1 and 10. Nearly 12 per cent (105) gave indices between 11 and 20; while 64, or 7.1 per cent, gave no index, showing that .2 c.c. of each of these sera contain too little complement and amboceptor to completely hemolyze this quantity of sheep corpuscle suspension.

It is to be noticed that the significance of a low hemolytic index by this technic is just the opposite from that in the Gradwohl method. Here a low index indicates that a serum is strongly hemolytic for sheep corpuscles while in the Gradwohl method, it shows the serum to have a low hemolyzing power.

Especial care must be exercised in determining the hemolytic index to make sure that the reading is sufficiently high. That is, if there is the least suspicion of any turbidity remaining in a tube when it is compared with one undoubtedly showing complete hemolysis, the one next higher in the series must be taken as showing the index. The importance of this is due to the fact that the exact amount of serum as determined by the index is to be employed in making the fixation test.

In obtaining the hemolytic index, our results do not agree with the statements usually made that the sera must be perfectly fresh in order to obtain the index. The 900 sera tested were, in the majority of cases, from twenty-four to forty-eight hours old, though the opportunity presented itself to secure them entirely fresh. At different times we have kept a serum for over a week and still secured an index, though at the end of this period this was somewhat higher than it was when the serum was fresh. The results obtained indicate that the serum, if kept aseptically and in an ice box, will give an index several days after it has been obtained, so that the test is applicable under the conditions ordinarily obtaining in making the routine Wassermann test in hospital laboratories. Presumably it will not prove applicable to sera which are sent from a distance, and accordingly are kept at room temperature for twenty-four hours or more.

The sera which gave no hemolytic index could not be tested by the method described without further modification. In nearly all of the cases here reported these sera were excluded as not being suitable for this test. More recently a method has been devised by which these also may be tested. This will be described later in this paper. The other sera, those giving a hemolytic index, were tested, after determining the index, as shown in Table II.

Each tube receives the serum to be tested and sheep corpuscles, and all except the first one, which is the serum control, also receive an antigen. It is to be recalled that this serum is not inactivated and, as shown in the table, is used in just sufficient quantity to com-

TABLE II  
MODIFIED TEST, USING THREE ANTIGENS

Tubes	1	2	3	4
Unheated serum		Indexed amount in each tube.		
5% sheep corpuscles		0.1 c.c. in each tube.		
Antigen, diluted	.0	0.2 c.c.	0.2 c.c.	0.2 c.c.
.85% saline solution		Up to .5 c.c. in each tube.		

Keep in water-bath at 37° C. for 30 minutes with occasional shaking. Read the results.  
The antigen used in Tube 2 was an alcoholic extract of human heart or guinea pig heart, half saturated with cholesterine; in Tube 3, alcoholic extract of the same tissue; in Tube 4, an acetone insoluble antigen.

pletely hemolyze the corpuscles present, but with no excess. There are, therefore, in each of the last three tubes, complement, anti-sheep amboceptor, antigen, sheep corpuscles, and, in cases of lues, syphilitic antibodies. The antigens must be strictly nonanticomplementary in the quantities used. As there is no period of heating at 37° C. before the corpuscles are added and so no appreciable lessening of the amount of complement present, it should follow that in all the control tubes and in all of the tubes where the complement is not very quickly fixed, hemolysis should occur. This result, we think, is shown by our tests. Also, that if hemolysis does not occur because of complement fixation in the syphilitic sera, the union, whatever its nature, between this natural complement, syphilitic antibody and lipoidal antigens must take place very much more rapidly than does that between the same complement, anti-sheep amboceptor and sheep corpuscles. This we believe to be a proper inference from our results.

Any serum which shows partial or complete lack of hemolysis in Tubes 2, 3, or 4 may then be tested by the scheme shown in Table III to determine the degree of inhibition. This test we have made with cholesterinized antigen only, as that is the most sensitive of the three antigens employed.

TABLE III  
MODIFIED WASSERMANN TEST, FINAL POSITIVE READING WITH CHOLESTERINIZED ANTIGEN

Tubes	1	2	3	4	5
Unheated serum		Indexed amount in each tube.			
Antigen, diluted	0	.2	.15	.1	.05
.85% saline solution		Up to .5 c.c. in each tube.			

The reading is made as in the routine Wassermann test, complete inhibition in Tubes 2, 3, 4 and 5, with complete hemolysis in Tube 1, being + + +.

Of the 900 sera which we have tested by this method, the first 231 were not carried through by the technic of Table II, but after determining the hemolytic index, they were tested only with a cholesterinized antigen as shown in Table III. The remainder were tested with three antigens and then the positive sera were tested as shown in Table III.

In several respects the technic as shown by Tables II and III closely parallel that of the routine Wassermann test as carried out by us. In this latter the total quantity in each tube is made up to .5 c.c. The amount of sheep corpuscles used in each tube is .1 c.c. of the 5 per cent suspension, and all sera are first tested with three antigens, using the same quantity as shown in Table II. All positive sera are then tested with the quantities of cholesterinized antigen as shown in Table III. The contrast between the modified test here described and the routine Wassermann test is seen, first, in the employment of the complement and amboceptor of the patient's own serum in the former and, secondly, in the omitting in the modified test of any preliminary incubation at 37° C. for the purpose of complement fixation.

In comparing the results of the modified test described and the routine Wassermann test, we have obtained in the 900 sera 64 which gave no hemolytic index. Of the remaining 836, there were 629

TABLE IV

POSITIVE READINGS WITH THE ROUTINE WASSERMANN TEST AND NEGATIVE WITH THE MODIFIED TEST IN 900 SERA\*

NO.	WASSERMANN TEST	MODIFIED WASSERMANN	HEMOLYTIC INDEX	SPECIFIC HISTORY
1	++±	0	6	Gastric ulcer, recurrent.
2	+++	0	6	Gastric ulcer, recurrent. Same as No. 1.
3	+±	0	6	Gastric ulcer, recurrent. Same as No. 1.
4	±	0	2	Brother of No. 1.
5	+++±	0	6	Pain in abdomen. Peritonitis.
6	±	0	12	Congenital lues. Wassermann 1 yr. ago, +.
7	++	0	10	Congenital lues. Other Wassermann tests ++ or +++.
8	++++	0	7	Husband said to have lues.
9	++++	0	5	Negative. Bichloride poisoning.
10	++++	0	6	Negative. Carbolic acid poisoning.**

\*For the sake of comparison, all tests showing even slight inhibition of hemolysis have been included in Tables IV, V, VI and VII.

\*\*One week later, both Wassermann and modified tests were negative.

which were negative by both tests, while 166 were positive by both tests. For the sake of comparison, all have been put down as positive which showed even slight inhibition of hemolysis. Thus, 795 agreed by both tests. Ten sera were positive with the routine Wassermann test and negative with the modified test described. Twenty-nine were positive with the modified test described and negative with

TABLE V

POSITIVE READING WITH THE MODIFIED TEST AND NEGATIVE WITH THE ROUTINE WASSERMANN TEST IN 900 SERA

NO.	WASSERMANN TEST	MODIFIED WASSERMANN	HEMOLYTIC INDEX	SPECIFIC HISTORY
1	0	++	4	Tabes. No history of primary.
2	0	++	5	Pulmonary stenosis.
3	0	+	6	Pulmonary stenosis. Same as No. 2.
4	0	++++	3	Congenital lues.
5	0	+++±	10	Primary, 1916.
6	0	+±	6	Hemiplegia.
7	0	+++±	3	Primary, 1916.
8	0	±	4	Loss of weight, pain in stomach.
9	0	+++±	4	Tabes. Spinal fluid, positive +±.
10	0	+±	6	Primary two years ago.
11	0	+++±	2	Gonorrheal arthritis, 1915.
12	0	++	4	Tertiary lues. Wassermann test, +++++.
13	0	++++	4	Furunculosis.
14	0	++	10	General paresis.
15	0	+	4	Tabes.
16	0	+++±	4	Cerebral syphilis. Wassermann positive two years ago.
17	0	++	5	Negative. Eczema.
18	0	+±	10	Tabes.
19	0	+++±	7	Negative. Hemiplegia.
20	0	++	5	Ulcers of leg.
21	0	±	4	Negative. Acute pleurisy.
22	0	±	4	Diagnosis is lues. Salvarsan treatment.
23	0	±	2	Negative. Furunculosis.
24	0	+	5	Negative. Arthritis.
25	0	+	12	No history obtained.
26	0	++++	12	Diagnosis, cerebellar tumor. Spinal fluid negative.
27	0	±	7	Same as 26. Made shortly after provocative salvarsan.
28	0	±	5	Wife has syphilis.
29	0	+++±	7	Tabes. Same as No. 18. Spinal fluid +++++.

the routine Wassermann test. In each of these cases a study of the history of the case was made when possible in order to determine which of the two tests gave the more reliable results. The summary of this study is given in Tables IV and V.

In examining these tables it is noticeable that, of the cases in

which the routine Wassermann test was positive and the modified test negative, only two gave a definite history of syphilis, one of these giving only a doubtful positive ( $\pm$ ) and the other being  $++$ . These were both cases of congenital lues. The husband of a third patient in this group was said to be syphilitic. Two of the sera

TABLE VI  
BOTH TESTS POSITIVE, MODIFIED METHOD GIVING THE HIGHER READING  
500 SERA

NO.	WASSERMANN TEST	MODIFIED WASSERMANN TEST	HEMOLYTIC INDEX	SPECIFIC HISTORY
1	++	++++	7	Negative. Necrosis, superior maxilla.
2	$\pm$	++	5	Primary, fourteen years ago.
3	$\pm$	++ $\pm$	13	Primary, ten years ago.
4	++	++ $\pm$	4	Negative. Infection, both hands.
5	$\pm$	+ $\pm$	10	Secondaries present.
6	$\pm$	+	4	Cerebrospinal lues.
7	$\pm$	++	4	Tabes. Salvarsan treatment.
8	$\pm$	++ $\pm$	7	Primary in 1911. Salvarsan treatment.
9	++ $\pm$	+++ $\pm$	15	Pneumonia.
10	$\pm$	+++ $\pm$	3	Congenital lues.
11	$\pm$	++	5	Primary, three years ago.
12	++ $\pm$	++++	3	Treatment for syphilis for two years.
13	$\pm$	+ $\pm$	5	Five abortions.
14	$\pm$	++ $\pm$	5	Pain in chest. Has had KI.
15	++ $\pm$	+++ $\pm$	7	Primary in 1915. Treated with mercury.
16	$\pm$	+++	2	Paraplegia.
17	$\pm$	++++	2	Primary, twenty years ago. Furunculosis.
18	++ $\pm$	++++	4	Tabes.
19	+ $\pm$	+++	2	Same as No. 17.
20	+	++	5	Tabes.
21	$\pm$	+++ $\pm$	10	Cerebral lues. Hemiplegia.
22	+ $\pm$	+++	4	Treated for lues.
23	$\pm$	+++ $\pm$	5	Primary in 1912. Salvarsan and mercury treatment.
24	+ $\pm$	+++ $\pm$	5	Hemiplegia.
25	+	+ $\pm$	2	Placenta suspicious of syphilis.
26	++ $\pm$	++++	10	Cerebrospinal lues.
27	$\pm$	+ $\pm$	4	Two stillbirths.
28	$\pm$	++++	4	Gumma of rectum. Previous Wassermann, ++++.
29	++ $\pm$	++++	4	Osteitis tibiae.
30	$\pm$	++++	5	Primary, four years ago.
31	$\pm$	+ $\pm$	6	Cerebrospinal lues.

giving a 4-positive were from cases of acute poisoning, and one of these, which was tested a week later, was then negative.

In Table V, twenty-nine sera which were positive with the modified test and negative by the routine Wassermann test came from

twenty-six patients. Twelve of these gave a history of syphilis or were suffering from diseases like tabes or general paresis which are recognized as being of luetic origin. Several of the others gave a + or  $\pm$ , a reaction too weak for a definite diagnosis, but they have been included here for the sake of comparison.

In the first 500 sera tested, there were 31 from 30 different patients in which a positive result was obtained by each method, but in which the modified method gave a higher reading than did the routine Wassermann, while in 9 sera the opposite was the case. These are given in Tables VI and VII.

TABLE VII

BOTH TESTS POSITIVE, ROUTINE WASSERMANN METHOD GIVING THE HIGHER READING. 500 SERA

NO.	WASSERMANN TEST	MODIFIED WASSERMANN TEST	HEMOLYTIC INDEX	SPECIFIC HISTORY
1	+++	++	5	Primary, twenty years ago.
2	++++	+++	2	Syphilis. Miscarriage.
3	++++	++	8	Epilepsy.
4	++++	+++ $\pm$	7	Myocarditis. Emphysema.
5	+++	+++ $\pm$	8	Primary, six months ago.
6	++++	++	7	Pain in feet.
7	++++	+++ $\pm$	11	Latent syphilis.
8	++++	+++ $\pm$	3	No history of primary. Has been treated for syphilis.
9	+++ $\pm$	++	12	Wassermann, positive (+) three years ago.

Of the 31 sera where the modified test gave a higher reading, 22 from 21 different patients gave a history of syphilis or the symptoms were such that a diagnosis of luetic infection had been made. In addition, one other patient had had five abortions, and in a third the placenta had an appearance which was considered suspicious of syphilis, while a fourth had osteitis of the tibia. Included in the above 22 were three cases of tabes, four in which the diagnosis of cerebrospinal syphilis had been made and one of congenital syphilis. The variation in the degree of complement fixation varied from  $\pm$  by the routine Wassermann with + + + + by the modified method to  $\pm$  by the former with + by the latter.

Of the 9 sera from as many different patients in which the routine Wassermann gave the higher reading, 6 gave a history indicative of syphilis. The greatest variation in the two readings here was



+ + + + to + +. A careful study of these Tables, IV, V, VI and VII, in which there is a discrepancy between the two tests, leads us to feel that the modified test in this series is not only more delicate than the routine Wassermann test but also that it is more accurate; also that it does not give an undue number of false positive tests. We appreciate, however, that false positive results do occur at times, even when these are 4-positive. Thus, No. 26 of Table V, a case diagnosed as cerebellar tumor, gave 4-positive by this method and negative by the regular Wassermann, but after a provocative dose of salvarsan, it became only a doubtful positive by the modified method, and a little later was entirely negative. Another case, too recent to be included in the 900 reported, gave similar results, and is improving under tuberculin treatment.

Among the 900 sera there have been six which were anticomplementary by the routine Wassermann method, using inactivated sera. Of these, two also failed to give any hemolytic index with the modified method. Of the other four, one, a case of staphylococcus septicaemia, gave a hemolytic index of four and was negative; one, a case of Banti's disease, gave an index of 6 and was negative; the third, carcinoma involving the bile ducts, gave an index of 6 and was negative; and the fourth, a case of congenital syphilis with treatment, with an index of 13, gave a weak positive.

The 64 sera, which gave no hemolytic index, came from a variety of conditions and did not appear to be particularly related to any one type of disease. In attempting to obtain the hemolytic index in samples of sera from placental blood and of spinal fluid, it was found that no hemolysis occurred. Either complement or amboceptor, or both were lacking. Until recently we have been unable to test these for the same reason that the other sera having no hemolytic index could not be tested. Recently we have found that by combining in equal quantities a negative serum having a comparatively low index, with a serum giving no index or with a spinal fluid, the combined serum or serum and spinal fluid, will give a hemolytic index and can be tested by the method described. We have as yet applied this to only a small number of sera having no hemolytic indices and to a small number of spinal fluids, but it apparently makes it possible to test any serum and any spinal fluid by this method. We have not had opportunity to apply it as yet to the serum from placental blood.

One evident criticism of the method as described is that the quantity of serum used in performing the test varies with different sera. Thus one serum may have an index of 3, in which case .03 c.c. of serum is used in each tube in making the test. Another serum, having a hemolytic index of 15, will have .15 c.c. of serum added to each tube. We anticipated that this would be a serious objection and that this larger amount of serum, when used in our routine Wassermann test, would give different results than would be obtained in using the ordinary amount, i. e., .02 c.c. Accordingly, series of Wassermann tests were made in which the indexed amount of serum was employed after being inactivated, this series being controlled by the routine Wassermann test, using .02 c.c. of serum. In no case in which the latter gave negative results did it change to positive when the larger amount of serum was used, even though the modified test gave a positive reaction. In a few positive cases, a slightly stronger positive was obtained for example, one giving + + + with .02 c.c. of the serum might give + + + + when the indexed quantity was employed. Our results indicate that no material change would have been obtained by the routine Wassermann method if the indexed amount of serum had been used in each case.

The rapidity of fixation of the patient's complement in the presence of lipoidal antigen and syphilitic antibody led us to try a similar technic, using the complement of guinea pig serum and antishoop amboceptor of serum from immune rabbits, with no preliminary period of incubation for complement fixation. Both the amboceptor and complement were carefully titrated and two series of tests were set up. In one of these, one unit of complement and one unit of amboceptor were added to each tube. In the second series, two units of each were added to each tube. The inactivated serum to be tested, antigens and sheep corpuscles were then added in the same quantities as in the routine Wassermann test, and placed in the water-bath at 37° C. for thirty minutes. In the first series, in which one unit only of complement and one unit of amboceptor were used, the serum controls hemolyzed while all of the tubes containing cholesterinized antigen, whether negative or positive by the routine Wassermann test, failed to show hemolysis, and several of the negative sera, tested by the other antigens, showed only partial hemolysis. Using two units each of complement and of amboceptor,

all of the serum controls hemolyzed and most of the tubes containing negative sera, in which the antigen was present, also hemolyzed. A few failed to hemolyze. The tubes containing the positive sera, which also contained antigen, did not hemolyze. There had evidently here been a rapid complement fixation as in the modified test described, but it was much less clear cut, and an excess of complement and amboceptor was necessary in order to produce hemolysis. The results are evidently much more delicate and reliable when natural complement and the antishoop amboceptor of the patient's own blood are used than they are when the guinea pig complement and rabbit antishoop amboceptor are employed.

#### SUMMARY

A modification of the Wassermann test is described which employs the natural complement and the antishoop amboceptor of the patient's own serum and in which there is no preliminary incubation at 37° C. for complement fixation. The method has been found to be more delicate than the routine Wassermann test and, according to the results so far obtained, is more reliable. It is not advocated as a method to replace the routine Wassermann test, but one to be given a trial paralleled with that test until its value is determined.

## A FEW POINTS ON PUBLIC PROPHYLAXIS AGAINST SYPHILIS

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IT is a source of the greatest satisfaction to see that the medical profession, disregarding its own interest, is opening a campaign against the dirtiest and the vilest of all the diseases—syphilis. If this disease would be like any other of the ordinary type, measles, scarlet fever, smallpox, or even tuberculosis, sanitary precautions would have been instituted and the spreading of the disease checked. It is, however, a disease which in the greatest number of cases is contracted by sexual intercourse and belongs, therefore, to the venereal diseases. Everybody who is infected with syphilis has the greatest interest to conceal the disease. Even before the physician when asked the question whether any venereal disease had been undergone, many patients yet deny, or at least, they say that they have never noticed anything.

*Why Syphilis is Concealed.*—This interest in concealing anything, which is connected with sexual gratification has to be attributed to that instinctive fear, to expose sexual processes, which is known as modesty. This is common to both sexes, but it is peculiarly developed in the woman. It forms her beauty in the psychical side, and when a woman has lost entirely the sense of modesty, she lacks also her sexual attractiveness. Yet among prostitutes and men of their kind the lack of fear of exposing feminine organs, makes strong sexual appeal.

Be it modesty or be it shame of confessing his or her guilt, everybody tries to conceal, and even to deny the existence or the presence of venereal diseases. A young prostitute in our hospital service, had a papular syphilide, and a thick eruption was at the edge of the hairy scalp and of the forehead. When she heard the diagnosis of secondary papular syphilide, she objected, and was explaining the presence of the papules as produced by herself pricking the skin with a pin.

This peculiar jealous feeling called modesty gives to love the aid of imagination, and imparts life to it. Mothers teach this feeling to

their little girls, while watching to the happiness of the future. Any indiscretion brings a remorse and is punished with the feeling of shame. In a well-educated woman the slightest infraction is punished with the atrocious shame. It is modesty which often leads to falsehoods, and modesty prevents the women being examined and relieved of their sufferings. Many women, rather than to expose their genitals and so be treated, prefer to suffer and let diseases take horrible headway.

The sense of modesty, the antipathy of being examined is greatly developed in half civilized people. Gradually as civilization increases this sense is overcome. This sense of fear prompts the woman to suffer pain, rather than to ask medical attention, when she has been unfortunately infected. It is for this reason that we find many women infected, who have not received any treatment. The diseases have advanced so much, that when these women are taken to the hospital, they are in the most miserable condition. Any other disease is easily found out, but venereal diseases are kept secret as long as it is possible.

Control of syphilis, therefore, is not a simple sanitary proposition as the control of scarlet fever, yellow fever; but it is a sociologic question, connected together with the sexual problems. Indeed, as Pusey<sup>1</sup> said in the solution of this problem we become immediately involved in that most difficult of social questions, the regulation of the relation of the sexes.

It is not possible to separate the idea of syphilis from venereal diseases. In practice some patients who have been accidentally infected with syphilis in a barber shop have tried to conceal their ailment just as strictly as those who have been infected in the sexual intercourse.

The fear and the sense of modesty in both sexes much more in the woman, together with the fear of being discovered infected with sexual disease, is a great stumbling block for any possible rule to control syphilis. Usually everybody is acutely sensitive to the judgment of others, and fear that the finding of a venereal disease will cause unfavorable opinion.

For this reason persons affected with venereal diseases must be found out by looking in their hiding places. They must be isolated and subjected to treatment until they are in condition not to spread the contagium.

*Dangers from Syphilis.*—The object of public hygiene is to preserve

the health of the people, so that human life may be prolonged to its natural end. Every life represents a capital for the state and for society, which assumes as a duty the preservation of the life in good health. A large number of individuals are rendered unable to work, and so to earn their living on account of the ravages wrought on them by syphilis and other venereal diseases, so much so that many are not only of no value because unproductive, but they represent a constant expense to the communities as objects of public charity.

That syphilis is at times spread accidentally—syphilis insontium—is true, and it has to receive strict attention from the health authorities. Some years ago seven cases of initial chancre on the chin and cheeks had been communicated in a barber shop, by the dirty epilation forceps, used for removing wild hair. Several young women showed infection from the mouth, tongue, tonsils, from kissing.

Several dentists, midwives, and doctors have been infected in the hands while making examination of patients, or performing operations. Yet we must state in a general way that the infection from syphilis and other venereal diseases is in 90 per cent of all cases through sexual intercourse. Ten per cent is from accidental and extragenital infection. In the statistics of the Cincinnati General Hospital in reference of syphilis to the occupation, we<sup>2</sup> found in ten years 875 domestics infected with syphilis, the largest number after the prostitutes. They had gone to the hospital unable to perform their duties. A cook or a dining room girl infected with secondary syphilis constitutes a serious danger for the family in which she is employed.

It is always dangerous to employ men infected with syphilis, at the condylomatous stage in factories and shops, and let them mingle with healthy boys and girls. Three cases of initial lesion of the lips occurred in a glass factory in three workmen, who received the infection from an infected companion through the glassblower. An initial lesion came on the lower lip of a little girl by blowing a tin horn, which had been in the mouth of a young man with mucous patches of the lips.

In general we can say that accidental infections of syphilis are reckoned at 10 per cent of all syphilitic infections, and the public has to be enlightened on the possible source of the contagium. Today with good sense, glasses and cups in shops, railroad cars and steam-

boats have disappeared and clean paper cups have been substituted.

The habit of drinking out of the same glass or cup, one after another, without rinsing, is dangerous. More dangerous yet is it to put in the mouth the cigar, a cigarette, or a pipe, which is often done by young men for joking. Kissing, too, is a possible source of contagion and has to be pointed out.

Illicit sexual relation, especially with prostitutes, is in most cases the means of syphilitic infection. Immorality and syphilis are the results of free prostitution.

*Surveillance of Prostitution.*—It is not our purpose nor the place to establish what constitutes a prostitute, what a licentious woman. Our purpose is to limit the spreading of the disease. If in any way the experience of others can give us some points, we can say that the Italian law to prevent venereal diseases has already given good results. In our professional practice we have occasion to attend many Italians. They have reached this country free from venereal diseases, and a short time after they have been here they are infected. They have had no idea of the danger of the infection. Some have served three years in the army, some have served in the campaign against Turkey in Tripolitania and Cyrenaica, and yet they had never had venereal diseases. Some are married; they have left wife and children in the old country under the obligation to send in due time the money to come to join them, and they find themselves ruined for life. There are, therefore, in the Italian legislation some points which, working for some years, have controlled the spreading of venereal diseases, while we in this country, hampered by narrow-minded good men and by hysterical old women, have remained looking at the fire, still discussing whether fire exists, and preventing anyone to throw a stream of water to stop the destruction.

From our personal experience we must say that the legislation for the prevention of venereal diseases in Italy, although not perfect, has already obtained a great benefit in checking the spreading of the social evil.

The principal points of the sanitary legislation in Italy are contained in the following laws: Crispi law, March 29, 1888; Nicotera law, October 27, 1891, and the present law, July 27, 1905. In all these laws all articles tending to restrict personal liberty have been abolished. The social defense against venereal diseases has been limited to the institutions of dispensaries, venereal wards in the

hospitals, and to the compulsory examination of the women inmates in public houses.

In force of the Crispi law the dispensaries for the treatment of venereal diseases in all important cities were entirely at the expense of the state. In 1898, 167 dispensaries in all important cities were treating patients suffering with venereal diseases. In 1901 by different disposition the dispensaries passed to the expenses of the communities, causing the suppression of all those that could not show a reasonable number of patients. After the law of July 27, 1905, authorizing the state to take charge of the dispensaries for venereal diseases, their number had increased to 102 in 1912.

From a relation of Truffi<sup>3</sup> to the Italian Society of Dermatology and Syphilology is shown that the dispensaries for the treatment of the venereal diseases had been distributed as follows: dispensaries belonging to communities, 62; dispensaries in connection with clinics, 1; dispensaries of the government, 1; dispensaries from charities, 9; dispensaries private, 1. In some cities dispensaries have been instituted by benevolent societies or by the city without the support of the state, 16 in number.

The law July 27, 1905, provides that in cities with a population above 40,000 free treatment has to be tendered in dispensaries for venereal diseases, from competent physicians to needy patients at the expense of the community. Moreover, in cities with less than 40,000 population the dispensaries for venereal diseases may be instituted mandatorily, if the hygienic condition requires.

The dispensaries and hospitals tendering treatment to venereal patients fail entirely in their mission if the ward and the dispensary are not under the direction of a specialist for those diseases.

It is the duty for all who have interest in this social problem to point out the omissions, the failures, and the inconveniences which occur in the actualization of the program of prophylaxis against venereal diseases. It has to be talked continuously and brought to the attention of the executive authorities, so that they may not rest in this subject as a thing done and perfected.

The hospitals for venereal patients in a contagious stage have to be supported by the state. In force of Article 11 of the law, 1905, the Department of the Interior enters in contract with the hospitals for the institution of venereal wards. The great inconvenience is that the government leaves the choice of the chief of the venereal wards to the hospital units, and often some physician incompetent



in handling these diseases is selected, assuming such a great responsibility.

The greatest importance is attached to the problem of the sanitary surveillance of the houses of prostitution. It is left to the mistress of the house to select the physician; and according to Article 14, she has to notify the health department of the selection of the physician by exhibiting a written acceptance of the physician, who in turn obliges himself to take the responsibility of the health of the inmates, and follow the instructions given by the authorities. The County Board takes necessary information on the physician and it will accept him or reject him and prescribe other conditions. Yet the health authorities have only the right to veto, and according to the law, they can not appoint the physician themselves. The physician appointed by the house is in a peculiar condition to recognize his client, and he is more inclined to shield the proprietor than not. As a consequence the surveillance in this way is only a partial protection in the prophylaxis.

In Italy, too, there are those who maintain that the state has no faculty at all to take up the hygienic surveillance of the houses of prostitution, on the ground that this surveillance organized by the state authorities affects the personal liberty of the women. Moreover, the idea that the women have been examined and found free from venereal diseases gives to the visitors a kind of guarantee and confidence, which can be against the purpose of hygiene.

Whenever the health of the public is in jeopardy, any scruple of interfering with the individual liberty or of religious order has to disappear. The words of Truffi on this subject are "that the sanitary surveillance of the houses of prostitution, although by many incidental circumstances can not in an absolute way prevent the diffusion of the venereal contagium, yet practically has contributed a great deal in the prophylaxis of these diseases."

Strict vigilance is the only way to obtain good results, but so long as the visiting physician is in common interest with the proprietor of the house this can not be fully obtained.

The sanitary service has to be given to physicians from the health department. They are selected from those who have large experience in venereal diseases.

As we have already stated, Italian immigrants coming to the U. S. have never been infected in their country, but they become infected when coming here looking for labor. Infected with syphilis and

gonorrhea, they take a little treatment, being ignorant of the consequences of these diseases. They are joined by the wives who are soon infected; continuously suffering in their health, they are breeding families of syphilitics.

This observation has become very much apparent, while years have gone by. We have not the time to collect data to present statistical tables, it is only from the patients themselves that we place our observations. We see those who had escaped infection in their native country, become infected in this country.

*Attack on Syphilis by Treatment.*—There is only one way to control syphilis, and this is by sanitary examination of the women practicing prostitution; when they are found infected they have to be kept in the hospital, isolated like any other contagious disease, treated carefully and released only when clinically cured. Of course to obtain a scientific cure would take too long a time; this can not be obtained in a short time. With the new antisiphilitic remedy, arsenobenzol, in two weeks we can state that all infectious manifestations have disappeared. The woman has to go to a dispensary and continue her mercurial treatment, and be constantly under observation, until she is considered scientifically cured.

Everybody agrees with Pusey and with Michael M. Davis on their views on the sanitary attack of syphilis. Skilled medical service, adequate equipment for diagnosis and treatment, well-organized clinics for patients and social service, and provision for evening clinics is really the ideal which we must reach. The great trouble is that diseased women do not go to a dispensary because they do not want to be seen, and yet are continuing in their call and are a focus of infection, dangerous to the welfare of the community.

It is necessary to go out and look for infected women. In our experience when in Cincinnati the police surveillance was established, every visit day from 19 to 25 women were sent to the venereal wards for treatment, and when the compulsory visit was removed, the female venereal ward was deserted, increasing a great deal the number of patients in the male venereal ward with the disabled men.

Prostitution is a plague, which can be considered coeval with society and is the greatest source of syphilis. It is against prostitution that all efforts must be directed. Public safety demands prophylactic measures to regulate the evil and prevent the spreading of syphilis. Vice in man, arising from natural impulse, is the first origin of prostitution. Lack of education, laziness, idleness, to-

gether with the stern problem of living on the part of the woman complete the work.

Chasing the women away from the houses of prostitution, scatters them in the residence districts of the cities, increasing the clandestine prostitution, which is the most dangerous and most detrimental in spreading venereal diseases. It is true that prostitution today in large cities has greatly changed, but the spreading of syphilis has not diminished.

It will appear that in the opinion of the writer, one of the greatest weapons to attack syphilis is a sanitary inspection of the women, done by a competent specialist for these diseases. No necessity for certificate: if the woman is found free from venereal, or syphilitic manifestation, she remains in her house or in the house of prostitution. When infected she is immediately taken to the hospital and subjected to heroic treatment. The woman infected with syphilis should not be released until the manifestations have entirely disappeared, and when released she should be under sanitary surveillance. With the new treatment of syphilis with salvarsan and mercury combined, in two or three weeks the syphilitic patient can be discharged, unless persistent symptoms should still remain, which is only found in rare cases.

*Writ of Habeas Corpus.*—The syphilitic woman has to be kept in the hospital, so long as manifestations capable of communicating the disease are present. In this interesting rule of prophylaxis, we have not very often been hampered by the court of law, with writ of habeas corpus.

Habeas corpus, as Judge Otto Pfleger remarked to me, is a high prerogative writ originating in the English common law, adopted by the United States, and recognized by the Statutes of the United States. Its great object is the liberation of those who may be imprisoned without proper authority. It issues as a matter of immediate right or complaint of the person imprisoned, or anyone else commanding the production of the body of the incarcerated person into court for the purpose of ascertaining whether without authority such person is restricted of his liberty. It issues against any official whether authorized in law or not to imprison persons, as well as against individuals and institutions. In other states it has been held, that in the absence of express authority granted by the legislature, a hospital can not retain a patient any longer than he desires to remain, where such patient has not gone to the hospital for the

purpose of isolation, or where he is not being constrained by the public authorities. 21 Cyc. of Law 1108. In the matter of Baker, 29 Howard Practice N. Y. 485, 130 Fed. Rep. 379.

The preservation of the public health is a necessary and proper exercise of the police power of the state, and the delegation of power to boards of health for the prevention of diseases is the usual and appropriate means to carry out its execution. The legislature of every state has appointed boards of health, or hospital authorities, granting them authority in the control of contagious and infectious diseases. The State of Ohio by law grants a city council authority to provide suitable hospitals for the reception and care of such persons as may be diseased and disabled, being under such regulation, and in the charge of such persons as the council may direct. (Sec. 3668—General Code.)

The legislature of Ohio also invested the board of health of a municipality with power to make such orders and regulations as it deems necessary for its own government, and for the public health and the prevention or restriction of diseases. A hospital or a board of health under either of these statutes has authority to pass reasonable regulations to control contagious and infectious diseases. But our own board of health has made provision for the supervision of infectious diseases. It has, however, been hampered by lack of funds in executing the work.

The Supreme Court of Ohio has not, so far as can be found, passed upon the exact question of the right to retain patients afflicted with venereal diseases in the hospitals against their will. Lower courts have had cases which turned upon the legality of any public official to make a charge for an examination of those afflicted with these diseases, to be paid out of certain public funds or by individuals as owners of property permitting their houses to be used by lewd persons.

In these cases the court concedes the right to control the infected parties in the interest of the health of the public and this is the main interest of the medical profession. The method of its proper execution must be left to the lawyers and to the public authorities.

I will use the exact words of Judge Pfleger: "In this advanced age the control of syphilis is no longer a question of religion or morals, it is a question of public health. If the good women, who are agitating the elimination of houses of ill fame will take the advice of the physicians, lawyers, and well-informed officials, that

proper governmental control and supervision, and isolation is the most effective remedy, they will be rendering mankind and future generations an enormous benefit."

*Consequences of the Suppression of the Public Houses.*—The statement of Wm. M. Sanger in the New York Board of Health is still true: "In common with other nations, we have passed laws intended to crush out prostitution: have made vigorous protests against its existence: and there our labors have ended." The experience acquired in this course of legislation only demonstrates that such laws can not be enforced, so as to produce the desired effect. The present mode of dealing with prostitution is really calculated to extend its prevalence, and instead of suppressing vice, drives it to seclusion, results different from the design, increasing the spreading of diseases.

The importance of sanitary and quarantine regulations is invaluable, and we can say it is a duty of the government to preserve and promote public health. Venereal diseases, and much more syphilis, ruin the health of the man of the family, diminish his efficiency, make an invalid, with the possibility of ending his life in an insane asylum.

Today with the new remedies we have at hand, with the new diagnostic means, we can obtain results which had not even been hoped for. Venereal diseases, and especially syphilis, with the effective therapeutics, with isolation of the patients, have diminished the number of diseases in Paris and in all cities where prophylaxis against venereal diseases has been enacted. In the same way from our personal observations venereal diseases in Italy have greatly diminished. When prostitution is driven to seclusion, nobody can help, and a diseased woman may infect several young men, making invalids and disabled, with risk for infection of other innocent people.

The woman who sells her graces when infected has to be sent to the hospital for efficient treatment. She has to be kept there for all time so long as she is a danger for communicating infection. Writ of habeas corpus has not any right to interfere with rules of public health. The hospital is not a prison, the woman is taken for treatment but under the act on contagious diseases she has not any right to the writ of habeas corpus. When we tried to retain in the hospital women infected with every kind of filthy diseases, a writ of habeas corpus, compelled us to release those pathologic specimens, and let them free to spread diseases broadcast.

We can say that the instruction and the education has done some good, but we can not reach everybody, and not everybody is capable of understanding the importance of syphilis.

We maintain with Sanger and with Truffi, that a regular medical visitation of the prostitutes forms the base of the attack on syphilis. When the woman is infected, she has to be taken to the hospital and treated until all manifestations have disappeared, and she is no more dangerous as a focus of infection.

What is to be said of the laws at present passed, with the view of crushing and dispersing prostitution. Years ago in every city, public and private places to visit girls were known. There was no danger of being trapped by the police; some sporting young men went once in a while to see their lady friend in order to gratify their sexual appetite. Between visitors were not only single men, but also married men, who on account of sickness of their wives or for other reasons needed to have some change and sexual gratification. When these houses were closed, the girl friends were driven to other places. The man who finds no more possible the gratification of his sexual instinct must of necessity look for some other clandestine ways. Here the factory girl, the working girls, and so on are taken as an aim, by means of presents and of promises, so as to have their graces. The motorcycle and the automobile have come to play a great role, and after a long ride and a little lunch, the way of gratifying the sexual instinct is easily found.

Here comes the trouble. The girl becomes pregnant, the girl wants to have the promise fulfilled, otherwise she will squeal. This is the reason for so many crimes. This is why girls are often found dead in canals, in cellars, etc., their lives are smothered for the only reason of avoiding the marriage, or the legal punishment. Nasher,<sup>4</sup> in referring to the prostitution as it was in 1886 and as it is in 1916, brought up many interesting points, showing the inexpediency and the dangers looming up from the suppression of prostitution. Thirty years ago American girls entered deliberately in fashionable brothels, because they wanted the association of men. Some had been in family way, and after being relieved they had been advised to enter in this life. Some were widows, and some married who had been disgusted with their husbands. Some daughters of well-to-do farmers, who had come to the city for work and had fallen into the hands of procuresses.

French, Irish, and German girls were imported for this purpose.

Scandinavian girls went into the lowest class of dives. Some made a little money, and went to the old country, some from one brothel to another, went down hill, ending in the tenderloin district.

It was estimated at those times in New York that there were 15,000 prostitutes, of whom about half were in the streets, one-third in the brothels, and the remainder received their selected patrons in their homes. Nasher claims that clandestine prostitution was very little, and little unchastity among respectable girls. At present street walkers have noticeably diminished, brothel houses have been practically wiped out, dives and resorts where prostitutes used to congregate, no longer exist, still there is a large number of professional prostitutes, clandestine prostitution is very prevalent, unchastity among apparently respectable girls very common. It seems that shop and factory girls are more frequently exposed, they are usually uneducated, weak-minded, credulous, and easily impressed by show of wealth.

In brief we can say with Nasher that the problem of prostitution is as unsatisfactory today as it was thirty years ago. There has been a vast improvement in the superficial moral aspect, but it has been secured by hiding vice in corners, where it can not be seen, and hence it has appeared in directions where it can not be followed. Professional prostitutes have gone back to clandestine prostitution, which is the most dangerous for the spreading of diseases, especially syphilis.

Since preventive measures have been established in any country venereal diseases have materially abated. By stringent prohibition the vice is driven into seclusion, and it is no more possible to watch and control the foci of infection.

A regular medical examination of all prostitutes is the only means of control of venereal diseases. This medical visitation has to be made by specialists in this kind of diseases, duly appointed by the health department, and sustained by the power of that department. The slightest symptom of disease should be sufficient evidence to warrant the removal of any woman to the syphilitic hospital. When a woman has been removed to the hospital, as a recognized syphilitic she has to be treated and thoroughly treated until the symptoms have disappeared. No writ of habeas corpus has to be placed to block the work of fighting syphilis. If a patient with smallpox is isolated in the hospital for contagious diseases, no court will issue a

writ of habeas corpus. In the same way when a woman infected with syphilis, knowing that she will infect any one with whom she comes in sexual contact, no writ of habeas corpus has to be issued. She is not imprisoned, she is only restrained to be treated and prevented from spreading disease.

It is only futile to imagine that forcing diseased women to submit to an examination and a specific treatment in a special hospital, causes undue interference with personal liberty. The right to commit a wrong, be it social, moral or physical, can never exist. The spreading of syphilis is a positive wrong, and a woman suffering from it, who will certainly spread the disease, is legitimately an object for compulsory treatment as a man with smallpox found roaming in the streets, has to be retained in the contagious diseases hospital.

*Surveillance of Lodging and Boarding Houses.*—The localities where working people go to room have to be under police surveillance. Immigrants, working people wandering in cities looking for labor and unable to find occupation, are always a danger. Idling about a city in search of a job, an immigrant may come in contact with conditions and with people of demoralizing influence and in this way lose his chance of becoming a useful citizen. He is in danger of becoming infected with syphilis and other diseases, thus becoming a charity seeker, and a dependent. The kind of houses in which immigrants go has direct effect on their health, morals, and efficiency. In general when going to a city looking for work a man does not find any too warm reception. He is not known, nobody knows anything about him, and if he has yet a few dollars the saloonkeeper, the poolroom proprietor, and inmates of disorderly houses may be friendly to him, so long as a few dollars of his savings last. These men have to be reached in some way. They have to know the dangers which lurk from syphilis, and for those people the dispensaries have to be open and accessible, at all hours. If they are found and can be treated in the dispensary so much the better, but when they are disabled and they are found dangerous, let them enter in the hospital and stay there until the danger of infection has passed. They must have the remedies free so that nothing hampers them to return to their former health. The money spent in this way by the community is well spent, to prevent spreading of the most abominable and dangerous of all diseases. Unfortunately the people at large



do not understand and with narrow ideas look only to those few dollars spent to relieve, and to help a poor unfortunate suffering all atrocious tortures, which they consider acquired from his own indiscretion. In the hospital salvarsan and neosalvarsan could not be administered unless the patient could pay \$5.00. With the ordinary mercurial treatment it took a patient four or five weeks to be in a decent condition to leave the hospital. By administering one full dose of salvarsan the patient could leave the hospital in two weeks. Calculating that a patient costs the hospital \$1.80 a day, which will be \$12.60 a week, by reducing the confinement from 4 to 2 weeks the price paid for the salvarsan will be amply repaid.

In conclusion we may say that the prostitution has to be well under the surveillance of the health department. A sanitary inspection of the women engaged in this kind of call is a necessity. Any woman following this kind of life when infected, has to be compelled to go to the hospital, and be treated until infectious manifestations have entirely disappeared. Dispensaries for treatment of venereal diseases have to be easily accessible, and the necessary remedies have to be given free to charity patients. Rooming houses, where immigrants are usually congregated, have also to be inspected, and suspicious women frequenting these places with good reasons have to be subjected to an examination, and when they have been found infected they must be compelled to isolation and treatment.

Venereal diseases, and especially syphilis, are the scourge of society, threatening the health not only of the man but of his wife and of his children; they reduce their efficiency, produce children who are weak, sickly, and bodily and mentally deficient. These diseases have to be checked and eliminated. Nothing has to be in the way, when we maintain that the health of the people is the grandest asset of a nation.

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## THE TECHNIC OF THE COMPLEMENT-FIXATION TEST FOR SYPHILIS\*

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IN answer to numerous inquiries regarding the technic employed by the writer in making the Wassermann test, or the complement-fixation test, for syphilis, the following paper has been prepared, giving in detail the technic which has been used during the past eight years, with very slight modifications. This technic is the one used in most of the laboratories maintained by the Medical Corps of the United States Army and has been thoroughly tried and possesses the merit of having been in use by several workers and tested out with thousands of cases, in the majority of which the test has been repeated at regular intervals, so that, had any irregularities occurred in the results obtained with the technic, they would have been discovered. It may be stated that in the hundreds of thousands of tests that have been made with this technic the results have been uniform and most satisfactory and it is believed that for simplicity and accuracy the technic here described has not been surpassed by any of the very numerous modifications of the Wassermann test.

The technic which follows was originally worked out by the writer and has been further improved by Lieut. Col. Vedder, of the Medical Corps, by originating apparatus especially suited for the test. It is a modification of both the original Wassermann method and of that of Noguchi, following Wassermann in using extracts of fetal syphilitic liver as one antigen and in inactivating the serum; and Noguchi in using a human hemolytic system instead of the sheep hemolytic system.

The following reagents are used in making the test:

1. *Complement*.—The fresh blood serum of guinea pigs.
2. *Amboceptor*.—The blood serum of rabbits immunized to human red blood corpuscles.

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\*From the Department Laboratory, Central Department, U. S. Army, Fort Leavenworth, Kansas.

3. *Antigens*.—An alcoholic extract of fetal syphilitic liver and a cholesterolized alcoholic extract of human heart muscle.

4. *Blood Corpuscle Suspension*.—A five or ten per cent suspension of human red blood corpuscles in normal (85%) salt solution.

5. *Blood Serum of Patient*.—Inactivated at 56° C. for one-half hour.

The preparation and titration of the reagents used will now be described in detail:

*Preparation and Titration of Complement*.—The complement consists of the blood serum of guinea pigs, as these animals vary considerably in the complementary strength of their serum, it is always best to use the blood serum from at least two pigs. If a few tests only are to be made, the guinea pig may be bled from the heart; a puncture being made into that organ with a hypodermic needle attached to a glass syringe holding 10 c.c. of blood and almost this amount can be removed from a full-grown pig without danger. The operation requires considerable practice and should be done with the pig etherized. After removal the blood should be ejected into a sterile Petri dish, allowed to stand at room temperature for two hours and then placed in an ice box overnight. In the morning the clear serum is pipetted off and diluted with an equal amount of salt solution (85%). It is best to rinse the needle and syringe out with salt solution before drawing the blood in order to prevent clotting in the needle; but this is not absolutely necessary.

If a large number of tests are to be made, it is better to sacrifice the pigs by cutting their throats, each pig being held over a Petri dish, the throat cut with a sharp knife or razor, after shaving, and the blood allowed to run into the dish. Great care should be taken not to cut too deeply, so as to penetrate the esophagus; for if the secretions of the stomach become mixed with the blood, the serum loses part, and sometimes all, of its complementary power. After collecting, the blood should be treated in the same manner as after puncture of the heart.

The syringe, needle, Petri dishes, and all apparatus used in collecting the blood should be sterile and perfectly dry, with the exception of the syringe which may be washed out with the salt solution, being careful to expel all of this solution before using the syringe, if accurate measurement of the quantity of blood collected is desired.

After pipetting off the serum from the clot, it should be diluted

with an equal amount of 85 per cent salt solution and this mixture constitutes the complement solution used in making the test. It should not be blood-stained and no red blood corpuscles should be present. If these are present, the mixture should be centrifuged and the blood corpuscles thus removed.

As this mixture of serum and salt solution varies markedly in complementary power at various times *it is absolutely essential, if accuracy is to be attained in the test, that it be titrated each day before it is used in the test.* It can be kept in an ice box for about three days and still be strong enough to use after titration; but usually upon the third, and almost always upon the fourth day, the titration will demonstrate that it has lost so much in complementary power as to be practically useless. The complement is at its best about thirty-six hours after withdrawal from the pig, but is much weaker immediately after withdrawal and grows gradually weaker from day to day after this period. Attempts have been made to preserve the complement by the addition of various substances, but none of the methods so far recommended have been generally adopted.

*Titration of the Complement.*—As stated, the complement mixture should be carefully titrated each day before it is used. If this is not done, grave errors will result in the test; and sera that should be positive may be rendered negative, or, what is more common, negative cases will give a false positive result. In making these titrations, as well as in making the test, either a 5 or 10 per cent suspension in 85 per cent salt solution of human red blood corpuscles may be used, but the writer prefers the 5 per cent solution as it is more economic of amboceptor, and this is the strength of the suspension which will be followed in describing the various titrations in this paper. After the complement has been diluted, as mentioned above, varying amounts are tested as shown in the following table, 10 test tubes, 100 by 12 millimeters, being used in the titration. (This is the size of test tube that is most convenient with the technic for the Wassermann test here described.)

After incubating in the water-bath at 37° C. for one hour, or in the incubator for two hours, at the same temperature, the tube that contains the smallest amount of complement showing complete hemolysis is noted and this amount is called one unit of complement. For instance, if it is found that Tube No. 4, containing 0.05 c.c. of complement is the first of the tubes to show complete hemolysis,

TABLE I  
TITRATION OF COMPLEMENT

TUBE NO.	AMOUNT OF SALT SOLUTION C.C	AMOUNT OF BLOOD SUSPENSION, 5% C.C	AMOUNT OF AMBOCEPTOR UNITS	AMOUNT OF COMPLEMENT C.C	Incubate in water bath at 37° C. for one hour and read. The tube showing complete hemolysis contains one unit of complement. Two units are used in making the test.
1	0.9	0.1	2	0.02	
2	0.9	0.1	2	0.03	
3	0.9	0.1	2	0.04	
4	0.9	0.1	2	0.05	
5	0.9	0.1	2	0.06	
6	0.9	0.1	2	0.07	
7	0.9	0.1	2	0.08	
8	0.9	0.1	2	0.09	
9	0.9	0.1	2	0.10	
10	0.9	0.1	0	0.10	

the tubes preceding it showing only partial hemolysis, then 0.05 c.c. of complement constitutes one complement unit, and in performing the test twice this amount, of 0.1 c.c. of the complement will be used for the dose of complement for each tube containing the same. In reading the titration if there is the slightest clouding in the fluid, hemolysis is not complete and the tube that is the first to show an absolutely crystal clear solution is the one that should be selected as representing one unit of complement. The control tube, Tube No. 10, which contains no amboceptor, should show absolute inhibition of hemolysis. If it does not, there is something wrong with the complement mixture or the salt solution used in making the titration.

*Preparation and Titration of Hemolytic Amboceptor.*—The hemolytic serum or amboceptor used in the Wassermann test as performed by the writer is prepared by immunizing rabbits to human red blood corpuscles. The human hemolytic system was adopted because it is believed that it gives the most accurate results with human blood sera and because it obviates the danger that is present of the action of the natural antisheep amboceptor normally present in human blood serum, and which sometimes interferes markedly with the accuracy of the test when the ordinary sheep hemolytic system is employed. It is not practicable, owing to the immense number of tests that are made in the army laboratories, to use any method which removes this antisheep amboceptor from blood serum; and, hence, it is much better for practical purposes to use the human hemolytic system. The only objection that can be urged against the

latter system is that it is slightly more difficult to immunize rabbits against human red corpuscles than against sheep corpuscles and that it requires a more careful technic both in collecting the blood and in injecting it into the animals, but this objection is of no really practical importance when the advantages of the human hemolytic system are considered.

Well grown, perfectly healthy rabbits are selected, preferably pure white ones, and are given repeated injections of washed human red blood corpuscles. The number of injections and their location vary with different workers, but the writer has found that the most rapid method of immunizing the animals and securing a good hemolytic serum is to give an intravenous injection, in the ear vein, of 1 c.c. of washed red blood corpuscles every other day until five or six injections have been given, when the rabbit's blood serum should be titrated and will generally be found strong enough in hemolytic properties to be used for the test. If not, two or three more intravenous injections of the washed red blood cells should be given. By this method it is comparatively seldom that an animal is lost, as the frequent injections prevent the development of anaphylactic phenomena, and a good amboceptor serum may be obtained in a reasonable period of time. The intravenous injections should be made very slowly and carefully.

Another good method is to give one subcutaneous injection of 5 c.c. of washed erythrocytes in the abdomen, followed by three or four intravenous injections in the marginal ear vein of 3 to 4 c.c. of washed erythrocytes, at intervals of from five to six days. This method often gives excellent results, but it is much slower and not infrequently we lose an animal from anaphylaxis during the process. The first method mentioned is preferable, but this method may be used where it is more convenient.

Whichever method is used, the rabbit's blood serum should not be tested for its hemolytic strength until from 7 to 9 days have elapsed from the date of the last injection of red corpuscles.

The blood corpuscles are prepared for the injections as follows: The requisite amount of blood (allowing at least twice the amount of blood as the amount of corpuscles to be used in the injections) is withdrawn from one of the large veins of the arm with a glass syringe, which has been sterilized and washed out with sodium citrate solution. After drawing the blood, it is at once ejected into a flask

containing from 200 to 250 c.c. of normal salt solution and distributed into large centrifuge tubes and centrifuged until the erythrocytes are deposited and the supernatant liquid is practically colorless. The supernatant salt solution is now carefully poured or pipetted off and the tubes again filled with fresh salt solution, well shaken so as to distribute the deposit of red cells throughout the solution, and again centrifuged. This process is repeated four times, when the supernatant salt solution is tested for albumin; if the merest trace is demonstrated, the washing is again repeated and continued until no reaction for albumin is obtained. Almost invariably four washings will be found sufficient. Care should be taken not to centrifuge for so long that the red blood corpuscles become tightly packed at the bottom of the centrifuge tubes, for the force necessary to dislodge them will break up a certain percentage and render them unsuitable for injection.

After the corpuscles are washed in the manner described they are mixed with as little normal salt solution as is necessary to secure a suspension that will pass through the needle of the injection syringe, and are at once injected either subcutaneously or intravenously with a sterilized syringe. From 7 to 9 days after the fifth or sixth intravenous injection has been given, if the first method of immunizing is used, or after the third or fourth intravenous injection, if the second method is used, the rabbit should be bled from the marginal ear vein into a Wright capsule or test tube, from 2 to 3 c.c. of blood being collected, the serum allowed to separate, and tested for its hemolytic strength. If it is not found strong enough, the injections may be resumed; and it will usually be found that one or two more will render the serum strong enough in hemolytic properties for use in the test. It is always well to start with at least three rabbits in preparing a hemolytic serum, in order to allow for the loss of one or more during the process.

The preliminary titration, just referred to, is easily performed in the following manner: A small amount of the rabbit serum is allowed to flow into a capillary pipette and one drop from this pipette is mixed with 39 drops of normal salt solution from the same pipette, thus giving a dilution of the serum of 1:40. The titration of the serum thus diluted is shown in Table II. The serum should be inactivated by heating at 56° C. before it is titrated or diluted.

TABLE II  
PRELIMINARY TITRATION OF AMBOCEPTOR SERUM

TUBE NO.	AMOUNT OF SALT SOLUTION C.C	AMOUNT OF COMPLEMENT UNITS	AMOUNT OF BLOOD SUSPENSION, 5% C.C	AMOUNT OF AMBOCEPTOR SERUM DIL. 1:40 DROPS	Incubate in water-bath at 37° C. for one hour or in incubator at same temperature for two hours.
1	0.9	1	0.1	1	
2	0.9	1	0.1	2	
3	0.9	1	0.1	3	
4	0.9	1	0.1	4	
5	0.9	1	0.1	5	
6	0.9	1	0.1	None	

If the unit of complement has not been determined by a previous titration, use 0.05 c.c. of a 1:2 dilution.

After incubating in the water-bath at 37° C. for one hour, or in the incubator for two hours, the titration is read, and if either the tube containing one or two drops of the serum is completely hemolyzed, the serum is strong enough for practical use in the test and the rabbit should be bled at once. Bleeding is done most quickly by cutting the carotid vessels while holding the animal over a large glass dish, into which the blood is allowed to flow. The neck of the rabbit, where the incision is to be made, should be shaved and washed carefully, but no disinfectant should be used. The glass dish should be sterilized before use and after the blood has been collected should be kept at room temperature for about two hours and then placed in the ice box overnight. In the morning the clear serum is pipetted off into small test tubes, inactivated by heating it for one-half hour in a water-bath at 56° C., and then kept in the ice box or suitable filter paper impregnated with the serum. It does not matter if the serum is slightly tinged with hemoglobin, as the amount used in the test is so small that it does no harm, so far as interfering with the reading of the reaction.

For eight years the writer has employed Noguchi's method of preserving amboceptor serum upon filter paper and the results have been so satisfactory that it has entirely displaced the use of the liquid serum in the army laboratories. Preserved in this manner the serum keeps much better and preserves its strength for a much longer time than when kept in the natural liquid form and there is no danger of infection. The method of preparing amboceptor paper is as follows:



The filter paper used for the purpose is Schleich and Schull's No. 597, but any other paper of approximately the same texture is as good. The paper is cut into squares measuring 10 by 10 centimeters, and actual experience has shown that it will take about 1.5 c.c. of the serum to saturate one of these squares of paper, so that it is an easy matter to calculate how many squares will be required for any given amount of rabbit serum. This number is placed, one by one, in a Petri dish containing the serum, and the process continued until all the serum is absorbed by the paper. The slips of saturated paper are then lifted carefully with a pair of forceps, thoroughly drained, and drawn across the edge of the dish a few times to remove any excess of serum, and then placed upon a piece of unbleached muslin, which should be large enough to contain all of the slips of paper. The muslin upon which the paper is laid is now placed under an electric fan and the paper rapidly dried, after which it should be placed in air-tight glass containers and kept at room temperature in a dark place.

The amboceptor paper thus prepared will keep for many months with very little loss of strength, although it is well to titrate the paper once a month. I have repeatedly used amboceptor paper a year old in practically the same dose as when it was first made, and paper two years old had only lost about one-eighth of its original strength at the end of that time.

*Titration of Amboceptor.*—The titration of the amboceptor paper is necessary in order to determine the amount that should be used in making the Wassermann test. After the papers are thoroughly dried a strip is cut from one of the sheets measuring 5 mm. wide

TABLE III  
TITRATION OF AMBOCEPTOR PAPER

TUBE NO.	AMOUNT OF SALT SOLUTION C.C.	AMOUNT OF COMPLEMENT UNITS	AMOUNT OF BLOOD SUS- PENSION 5% C.C.	AMOUNT OF AMBOCEPTOR PAPER M.M.	Incubate in water-bath at 37° C. for one hour or in in- cubator for two hours at same temperature.
1	0.9	1	0.1	5 by 1	
2	0.9	1	0.1	5 by 2	
3	0.9	1	0.1	5 by 3	
4	0.9	1	0.1	5 by 4	
5	0.9	1	0.1	5 by 5	
6	0.9	1	0.1	None	

If the unit of complement has not been determined against a known amboceptor by titration, use 0.05 c.c. of a 1:2 dilution of the complement as the unit.

and varying lengths of this are used in the titration, as shown in Table III. The outer edge of the saturated sheet of paper should be trimmed off before cutting the strip to be titrated, in order to avoid any concentration of the serum which might occur at that portion of the paper.

After incubating in the water-bath at 37° C. for one hour, or in the incubator at the same temperature for two hours, the tubes being shaken every fifteen minutes in order to facilitate the liberation of the amboceptor serum, the titration is read and the first tube to show complete hemolysis is noted and the amount of paper contained in that tube is called one unit of amboceptor. A good amboceptor paper should show complete hemolysis in tubes Nos. 2 or 3, or with pieces of paper measuring 5 by 2 or 3 millimeters. Often the first tube will show complete hemolysis and, when this occurs, in order to use the paper one must increase the strength of the blood suspension and this is generally done by using a 10 per cent suspension instead of 5 per cent suspension. The control tube, No. 6, should not show any hemolysis. In making the test two units of amboceptor paper are used. For instance, if one unit was found by titration to be a piece of paper 5 by 2 mm. a piece 5 by 4 mm. would be used in making the test.

As already stated, before impregnating the filter paper, it is necessary that the blood serum be inactivated by heating it for one-half hour at 56° C. in the water-bath, in order to get rid of the complement.

*Preparation and Titration of the Antigens.*—As is well known, a great many substances have been used as antigen in the Wassermann test, but in the army we have found that alcoholic extracts of fetal syphilitic liver and cholesterinized alcoholic extracts of normal human heart muscle have given the most satisfaction and the preparation of these will here be described. The acetone insoluble lipoid antigen of Noguchi is also used at times, in conjunction with the other antigens mentioned, but not as a routine measure in most of our laboratories.

*Preparation of Alcoholic Extract of Fetal Syphilitic Liver.*—A fetal liver rich in spirochetes is selected, washed free from blood, and any fat present removed. One hundred grams is weighed out, all blood removed by thorough washing, and cut into very small pieces, or better, run through a meat grinder. The material is then placed in

a suitable bottle, or other container, and 1000 grams of absolute alcohol added, and the whole is then placed in an incubator at 37° C. for 10 days, being thoroughly shaken three times a day, when it will be ready to titrate. If a shaking machine is available, the material, after adding the alcohol, is placed in a suitable bottle and shaken for 24 hours at the end of which time it will be found to be thoroughly extracted. After extraction is completed, the material is filtered through filter paper and the filtrate evaporated to two-thirds its original volume and titrated.

*Preparation of Cholesterinized Heart Extract.*—The same method is used in preparing the alcoholic extract of heart muscle, the material being washed free from blood, all fat removed, and 100 grams of the heart muscle being cut into small pieces or run through a meat grinder and extracted with absolute alcohol in the same proportions (1000 grams of absolute alcohol to 100 grams of muscle). After extraction the material is filtered through paper, evaporated to two-thirds its original volume, again filtered through filter paper, and 0.4 per cent of cholesterin added. This gives a saturated solution of cholesterin and there is generally an excess of cholesterin left after standing, and in using the antigen care should be taken not to get any of this excess in the pipette used in the work and thus in the diluted solution of the antigen. After the addition of the cholesterin the antigen is placed in glass stoppered bottles and kept in an ice box. It is very essential that all antigens be kept in an ice box as they rapidly lose strength if kept at room temperature.

*Titration of Antigens.*—Antigenic extracts lose strength with more or less rapidity, so that it is not only necessary to make a primary titration in order to determine their value, but such titration should be repeated at least once in two or three weeks if accurate results are to be obtained, unless it is found that the particular antigens employed are very stable, when monthly titrations will be sufficient. A really good antigen loses strength slowly and the writer has often worked with extracts that were practically as strong in antigenic qualities after several months as when first made, but the reverse is often true and an antigen will be found that rapidly loses strength, and thus frequent titrations are advisable.

The antigenic extract must be titrated with a known syphilitic serum in order to determine its antigenic properties; with a normal serum in order to demonstrate that it will not inhibit hemolysis

when used with such a serum; and in the absence of either a normal or syphilitic serum, in order to determine whether or not it is anti-complementary or hemolytic by itself. Before titrating, the antigen should be properly diluted, which is accomplished by adding one part of the extract to nine parts of normal salt solution. Any antigenic extract prepared in the manner just described and diluted so as to produce an emulsion containing one part of the extract to nine parts of salt solution, that is neither anticomplementary or hemolytic of itself or in the presence of a normal serum in a dose of 0.2 c.c., and that gives complete inhibition of hemolysis in the presence of a syphilitic serum in a dose of 0.05 or 0.1 c.c., will be found to give satisfactory results in practice.

Table IV illustrates the titration of antigenic extracts for the purpose of determining their hemolytic properties. The quantities of antigenic solution tested have been determined by a large number of experimental tests to yield satisfactory results.

TABLE IV  
TITRATION OF ANTIGEN FOR HEMOLYTIC PROPERTIES

TUBE NO.	AMOUNT OF SALT SOLUTION C.C.	UNITS OF COMPLEMENT	AMOUNT OF ANTIGEN EMULSION C.C.	AMOUNT OF BLOOD SUS- PENSION 5% C.C.	Incubate in water-bath at 37° C. for one hour or in in- cubator for two hours.
1	0.9	2	0.05	0.1	
2	0.9	2	0.10	0.1	
3	0.9	2	0.15	0.1	
4	0.9	2	0.20	0.1	
5	0.9	2	None	0.1	

If the complement has not been titrated, use 0.05 c.c. of a 1:2 dilution as one unit.

In the above titration none of the tubes should show hemolysis. If hemolysis occurs in all, including Tube 5, the control tube without antigen, it would indicate that hemolytic substances were present either in the complement or blood suspension, or both; but if hemolysis should occur in one or more of the tubes containing antigen, the control tube remaining unhemolyzed, it would demonstrate that the antigen is hemolytic; and, in this event, it should be discarded unless, upon being further diluted, it is found to give satisfactory results. If none of the tubes containing antigen show hemolysis, it demonstrates that the antigen is not hemolytic and, therefore, so

far as hemolytic properties are concerned, safe to use in making the Wassermann test.

The method of titrating the antigenic emulsion in order to ascertain whether or not it is anticomplementary is shown in Table V, which follows:

TABLE V  
TITRATION OF ANTIGEN FOR ANTICOMPLEMENTARY PROPERTIES

TUBE NO.	AMOUNT OF SALT SOLUTION C.C.	UNITS OF COMPLEMENT	AMOUNT OF ANTIGENIC EMULSION C.C.	AMOUNT OF BLOOD SUSPENSION 5% C.C.	UNITS OF AMBOCEPTOR PAPER	Incubate in water - bath at 37° C. for one hour or in incubator for two hours.
1	0.9	2	0.05	0.1	2	
2	0.9	2	0.10	0.1	2	
3	0.9	2	0.15	0.1	2	
4	0.9	2	0.20	0.1	2	
5	0.9	2	None	0.1	2	

As the result of this titration there should be complete hemolysis in all of the tubes. If Tube 5, the control tube, should show inhibition of hemolysis, it would demonstrate that either the complement, amboceptor, or blood suspension, was inhibitory, but if any of the tubes containing antigen show inhibition, the control tube being hemolyzed, it would demonstrate that the antigen is anticomplementary, and under such circumstances it should not be used for the test.

Having tested the antigen for its hemolytic and anticomplementary properties, it is now necessary to test it with a known positive serum to determine its antigenic properties, and with a known normal serum in order to demonstrate that it will not give positive results with nonsyphilitic sera in doses which are found to be antigenic with the syphilitic serum. This titration is illustrated in Table VI, which follows:

As the result of this titration all of the tubes containing the antigen should show complete inhibition of hemolysis where syphilitic serum is present, and complete hemolysis where normal serum is present. Thus Tubes 1, 2, 3, and 4 should show absolute inhibition of hemolysis, while Tube 6 should show complete hemolysis. If Tube 6 shows any trace of inhibition, the antigen is not suitable and should be discarded; and the same is true if there is less than complete inhibition of hemolysis in Tube 2. There may be a slight trace of hemolysis in Tube 1, containing only 0.05 c.c. of the anti-

TABLE VI

TITRATION OF ANTIGEN TO DETERMINE ANTIGENIC PROPERTIES

TUBE NO.	AMT. OF SALT SOLUTION C.C.	AMT. OF LUTETIC SERUM INACTIVATED C.C.	UNITS OF COMPLEMENT	AMT. OF ANTIGENIC EMULSION C.C.	Incubate in water - bath at 37° C. for 30 minutes or in incubator for one hour.	AMT. OF BLOOD SUSPENSION 5% C.C.	UNITS OF AMBOCEPTOR PA-PER	Incubate in water-bath for one hour or in incubator for two hours at 37° C.
1	0.9	0.1	2	0.05		0.1	2	
2	0.9	0.1	2	0.10		0.1	2	
3	0.9	0.1	2	0.15		0.1	2	
4	0.9	0.1	2	0.20		0.1	2	
5	0.9	0.1	2	None		0.1	2	
6	0.9	Normal serum, 0.1	2	0.20		0.1	2	
7	0.9	Normal serum, 0.1	2	None		0.1	2	
8	0.9	None	2	None		0.1	None	
9	0.9	None	2	None		0.1	2	

genic emulsion without harm; but it will always be found better in practice to use only those antigenic extracts that give complete inhibition of hemolysis with 0.05 c.c. of the dilution. Tube 7, which is a control of the normal serum used, should show complete hemolysis, and if not, another normal serum should be tested. Tube 8, the control of the complement, should show complete inhibition of hemolysis; and Tube 9, the control of the hemolytic system, should show complete hemolysis.

If these results are obtained, the titration demonstrates that the antigen, as diluted, is suitable for use in the Wassermann test, in that it produces absolute inhibition of hemolysis in the presence of syphilitic serum in a dose as small as 0.05 c.c., and that it does not inhibit hemolysis in the presence of a normal serum in four times that dose. Such an antigen is suitable for use in the Wassermann test.

The amount of antigenic emulsion necessary to produce complete inhibition of hemolysis in the presence of a syphilitic serum is known as an antigen unit and in the test only one antigen unit is employed. *The unit is not doubled in making the test as is the unit of complement and amboceptor.* An antigenic extract that gives complete inhibition of hemolysis, in the presence of syphilitic serum, in a dose

of 0.05 c.c. of a 1:10 dilution, is preferable for use; but one giving the same result in a dose of 0.1 c.c. of a 1:10 dilution will be found satisfactory in practical work.

As the antigen rapidly loses strength if kept at room temperature, it should always be kept in the ice box, when not in use, and should be titrated preferably before each series of tests, but once a week will be found sufficient in practice, and most well-made extracts do not show much loss in strength, if kept in the ice box, after even two or three months. This is especially true of cholesterinized antigens.

*Preparation of the Blood Suspension.*—In the complement-fixation test for syphilis as performed by the writer, each tube contains 0.1 c.c. of a 5 per cent suspension of red blood corpuscles in 85 per cent salt solution. Originally 0.1 c.c. of a 10 per cent suspension was used, but it was found that a 5 per cent suspension gave just as satisfactory results, and was much more economic of amboceptor. The blood suspension is prepared as follows:

The quantity of blood required for the tests will depend, of course, upon their number. One cubic centimeter of blood will furnish enough suspension for nearly one hundred tests, and unless one is doing a very large number of tests, enough blood may be easily obtained by constricting the middle finger, after forcibly swinging the arm for a few times, with a rubber tourniquet or piece of tubing and pricking the finger upon the dorsal surface just above the root of the nail with a sterile needle or glass point. The blood is allowed to drop into sterile graduated centrifuge tubes, each tube being filled with normal salt solution (85%) up to the 9 c.c. mark, until the tube is filled to the 10 c.c. mark. The tube is then shaken well and centrifuged until all the corpuscles are collected at the bottom. The supernatant liquid is then carefully poured or pipetted off, the tube again filled with salt solution, and again centrifuged until the cells are all at the bottom of the tube. This process is repeated until the corpuscles have been thus washed four times, which will be found sufficient.

The supernatant fluid is poured off for the last time and the amount of red blood corpuscles noted and the tube filled with enough salt solution to make a 5 per cent suspension. Thus if there is 0.5 c.c. of red blood corpuscles at the bottom of the tube, it would require 9.5 c.c. of salt solution to make a 5 per cent suspension.

In the test, 0.1 c.c. of this suspension is added to each tube, which contains 0.9 c.c. of normal salt solution, thus making a half of one per cent suspension. This makes a suspension sufficiently strong to render the reading of the test easy and is much more saving of amboceptor than the use of a stronger suspension.

The blood corpuscle suspension must be kept in the ice box when not in use as it hemolyzes rapidly if kept in a warm room. It should preferably be prepared fresh each day, but if kept in a good ice box it may be used for two, and even for three days, in some instances, but it must be used in titrations before each series of tests in order to ascertain the amount of complement necessary to compensate for the loss in the resisting powers of the blood corpuscles when thus kept, even in an ice box.

*Collection of the Patient's Blood.*—Many methods have been advocated for collecting blood for the Wassermann test and much special apparatus has been devised for this purpose. The simplest and best method is to remove from 2 to 5 c.c. of blood from one of the large veins in the forearm or at the bend of the elbow with a properly sterilized glass syringe. The arm should be cleaned, the site of the puncture with the needle brushed with iodine, and the needle, held almost parallel with the surface of the arm, pushed through the skin and directly into the vein. A very little practice will result in anyone becoming an expert in this procedure and it will be found much more convenient than the use of the Wright capsule or many of the special forms of apparatus which have been devised. After withdrawing the amount of blood mentioned, it is ejected into a suitable vial, the serum allowed to separate, after which it is pipetted into a sterile tube or small vial if it is to be mailed, or used at once in the test. Control sera should always be kept in the ice box when not in use.

The Keidel tube is an excellent, although rather an expensive method of collecting blood for the Wassermann test. These tubes can be obtained from laboratory supply houses and are superior, in the writer's opinion, to any of the other forms of special apparatus. However, all that is needed for this work is a glass syringe of requisite capacity and a small vial in which to place the blood when it has been withdrawn.

*Technic of the Test.*—The method of performing the Wassermann test here described has been found the most simple and adaptable



method for army practice and possesses the virtue of great accuracy as proved by nearly ten years use and the comparison of results from different laboratories in many thousands of cases.

The serum used for testing must invariably be inactivated by heating it in a water or paraffine bath at  $56^{\circ}$  C. for one-half hour, and all of the titrations in which serum is used must be made with inactivated serum, as has been described. This is very important, for alcoholic extracts are used as antigens, and such extracts often give false positive results if serum which has not been inactivated is tested.

Test tube racks containing two parallel rows of holes should be used, and test tubes measuring 100 by 12 mm. will be found most convenient.

Before making each series of tests the complement should be carefully titrated as already described. Some authorities prefer to titrate the amboceptor instead of the complement, but as the complement is the substance in the test that is most apt to vary in strength, it should be titrated in preference to the amboceptor. As a matter of fact, the titration of the complement with a fixed dose of amboceptor can not result in any fallacies in the test, as the amount of complement found necessary to produce hemolysis with the dose of amboceptor used, when doubled, is always sufficient to give accurate results when used in the test.

For each serum to be tested two tubes are necessary, an anterior and a posterior one. The anterior tube contains the serum together with the syphilitic antigen, while the posterior contains the serum without antigen, thus acting as a control of the serum tested. Besides these two tubes there must be a control set of two tubes for a known syphilitic serum, and a control set of two tubes for a known normal serum, the anterior tubes in each set containing the antigen, while the posterior tubes contain no antigen, and thus control the sera tested. All sera used in the test must be inactivated by heating in a water or paraffine bath at  $37^{\circ}$  C. for one-half hour.

In making the test proceed as follows: In each of the tubes enumerated, place 0.9 c.c. of normal salt solution. In Tube 1, anterior, place 0.1 c.c. of the serum to be tested and the same amount in Tube 1, posterior. In Tube 2, both anterior and posterior, place 0.1 c.c. of the known syphilitic serum. In Tube 3, both anterior and posterior, place 0.1 c.c. of the known normal serum. Now add to

each tube *two* units of the complement, and to each *anterior* tube one unit of the antigen, and incubate in a water-bath at 37° C. for one-half hour, or in an incubator for one hour at the same temperature. At the expiration of this time, add to each tube 0.1 c.c. of the suspension of human red blood corpuscles and *two* units of the amboceptor paper. Incubate for one hour at 37° C. in the hot water-bath or for two hours in the incubator at the same temperature, place in the ice box for one hour, and then read the results. After the amboceptor paper is added, the tubes should be well shaken every fifteen minutes during the incubation, in order to liberate the serum from the paper. Neglect of this will result in partial positive reactions in sera that should react negatively.

If desired a hemolytic and antigenic control tube may be included but this is not necessary in practice if titrations of the complement have been made prior to the test, as this titration will show if anything is wrong with the hemolytic system. An antigen control may be employed if the antigen has not been titrated recently.

The following table illustrates the method of making the test which has been described:

TABLE VII

METHOD OF PERFORMING THE COMPLEMENT-FIXATION TEST FOR SYPHILIS

SERUM FOR DIAGNOSIS	POSITIVE CONTROL SET	NEGATIVE CONTROL SET			
ANTERIOR TUBES	ANTERIOR TUBES	ANTERIOR TUBES			
Patient's serum. 0.1 c.c.	Positive serum. 0.1 c.c.	Normal serum. 0.1 c.c.	Incubate for one-half hour at 37° C. in water-bath or for one hour in incubator at same temperature.	Add two units of amboceptor paper to each tube and 0.1 c.c. of 5% suspension of human red blood corpuscles.	Incubate for one hour at 37° C. in water-bath or for two hours in incubator at same temperature.
Complement. 2 units.	Complement. 2 units.	Complement. 2 units.			
Antigen. 1 unit.	Antigen. 1 unit.	Antigen. 1 unit.			
Salt solution. 0.9 c.c.	Salt solution. 0.9 c.c.	Salt solution. 0.9 c.c.			
POSTERIOR TUBES	POSTERIOR TUBES	POSTERIOR TUBES			
Patient's serum. 0.1 c.c.	Positive serum. 0.1 c.c.	Normal serum. 0.1 c.c.			
Complement. 2 units.	Complement. 2 units.	Complement. 2 units.			
Salt solution. 0.9 c.c.	Salt solution. 0.9 c.c.	Salt solution. 0.9 c.c.			

If all the reagents used in the test are working properly the result should be as follows: The anterior tube, containing the patient's serum, if syphilis is present, should show complete inhibition of hemolysis (positive reaction), while the posterior tube containing the patient's serum, but with no antigen present, should show complete hemolysis. Of course, various degrees of inhibition will be shown in the anterior tube if the case is an early one, treatment has been given, or if the reaction is weak. If the patient's serum is normal there should be complete hemolysis in the anterior tube as well as in the posterior tube. The posterior, or control tube of the patient's serum, should always show complete hemolysis.

The anterior tube of Set 2, containing a known syphilitic serum, should show complete inhibition of hemolysis (positive reaction) while the posterior tube should show complete hemolysis. If the posterior tube shows any inhibition, it demonstrates that the positive control serum is unsatisfactory.

The anterior tube of Set 3, containing the known normal serum, should show complete hemolysis, as should the posterior tube of this set. If a control tube for the antigen and for the hemolytic system be used, both should show complete hemolysis.

*The Reading of the Results.*—The results of the Wassermann test are variously reported from different laboratories. Thus the nomenclature applied to the results of the test may vary, and unless one is acquainted with the meaning of the various terms applied to the various degrees of the reaction, grave errors may occur in the application of the results of the test in diagnosis.

In perhaps the majority of laboratories the results of the test are recorded as four plus (+++), indicating complete inhibition of hemolysis, and therefore, a positive reaction; three plus (+++), two plus (++), and plus (+), indicating lesser degrees of inhibition of hemolysis, and, therefore, more or less doubtful reactions. In the army only four designations are employed in reading the test and in reporting the results; i. e., double plus (++), indicating complete inhibition of hemolysis and, therefore, a positive reaction; plus (+) indicating anything between complete inhibition and 50 per cent of inhibition of hemolysis; plus-minus ( $\pm$ ), indicating anything between 50 per cent of inhibition and complete hemolysis; and minus or negative, indicating complete hemolysis, and therefore, a negative result. Plus and plus-minus reactions are always considered doubt-

ful reactions in the absence of a clear history of infection or if definite clinical symptoms of the disease are not present.

Comparing our nomenclature with that first mentioned, the three and two plus reactions would correspond with our plus reaction, the one plus with our plus-minus reaction, and the four plus with our double plus reaction.

As we have stated, the method of performing the Wassermann test here described has been given a very thorough trial in army laboratories and has been found to give perfectly satisfactory results, and it is believed that it is as well adapted to civilian laboratories and will be found at once simple and accurate.

## EPOCH-MAKING CONTRIBUTIONS TO THE STUDY OF SYPHILIS

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### I. JOHN HUNTER

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#### Of the Poison Being the Same in Gonorrhea and in Chancre\*

IT has been supposed by many that gonorrhea and chancre arise from two distinct poisons; and their opinion seems to have some foundation, when we consider only the different appearances of the two symptoms, and the different methods of cure; which, with respect to the nature of many diseases, is too often all we have to lead our judgment. Yet, if we take up this question upon other grounds, and also have recourse to experiments, the result of which we can absolutely depend upon, we shall find this notion to be erroneous.

If we attend to the manner in which the venereal poison was communicated to the inhabitants of the islands of the South Seas, there are many circumstances which tend to throw light upon the present question. It has been supposed, as no mention is made of a gonorrhea at Otaheite, that it must have been the chancre that was first introduced into that island, and that, of course, nothing but chancre could be propagated there; for as no gonorrhea had been communicated, no such disease could take place. But if we were to reason upon all the probable circumstances attending the voyages to that part of the world, we should conclude the contrary; for it was almost impossible to carry a chancre so long a voyage without its destroying the penis; while we know from experience that a gonorrhea may continue for a great length of time. It is mentioned in Cook's voyage, that the people of Otaheite who had this disease went into the country and were cured; but when it became a pox it was then incurable. This shows that the disease which they had must have been a gonorrhea, for we know that it is only a gonorrhea that can be cured by simple means; and further, if it

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\*A Treatise on the Venereal Disease, Part I, Chap. 1, Sec. 5.

had been a chancre, and they had been acquainted with the means of curing it, they could also have cured the lues venerea.

Wallis left Plymouth in August, 1766, and arrived at Otaheite in July, 1767, eleven months after his embarkation; and, if none of his men had the disease when he sailed, there was hardly a possibility of their contracting it anywhere afterwards in the voyage. This appears to be too long for a gonorrhea to last. But let us suppose even that Wallis carried it thither in his ship, one or two of his crew having the disease: as he stayed there five weeks, it was very possible, even probable, that such person or persons might have communicated it so quickly as to have become the cause of contamination of the whole crew of his ship. But as this did not happen, it is a presumptive proof that Wallis did not carry it thither.

Bougainville left France in December, 1766; but he touched at several places where some of his people might have got the disease, the last of which places was Rio de la Plata, which he left in November, 1767, and arrived at Otaheite in April, 1768, five months after. This interval of time agrees better with the usual continuance of the disease than the length of Wallis's voyage; and, therefore, from this circumstance it becomes more probable that Bougainville carried it thither. Besides, it is likely that he could guard his people less against the disease than Wallis; for Wallis could have his choice of men at his first setting out, which was all that was necessary to prevent his carrying the disease with him, for he ran no risk of contracting it afterwards; but although Bougainville had the same advantage at first, yet he had it not afterwards, for his men were in the way of infection in several places, and he had no opportunity of changing them, and probably no great chance of having them cured. The circumstance of the disease being found by Bougainville at Otaheite soon after his arrival is a kind of proof that he carried it thither himself: for I observed before, that if Wallis had carried it by one man only, this man could have, in a very few days, so far propagated it as to have spread it through the whole ship's crew; and as Bougainville arrived at the island ten months after Wallis, there was a sufficient time for the inhabitants of the whole island to have been infected, and the ravages of the disease must have been evident to them immediately after their arrival. Bougainville remained only nine days at the island of Otaheite, and observed nothing of the disease till some weeks after his

departure, when it was found that several of the crew were infected, which most probably must have happened in consequence of the poison being carried there by some of his own people. It is also mentioned by Cook that the Otaheiteans ascribed the introduction of the disease to Bougainville; and we hardly suppose that they would be so complaisant to our countrymen as to accuse Bougainville, when they must have known whether the disease was imported by Wallis or not, especially as they had no reason to be partial in favor of the people who accompanied the latter. But as we find in Cook's last voyage that the disease in every form is now there, and as we have no new intelligence of a new gonorrhea being since introduced, we must suppose that every form of the disease has been propagated from one root, which most probably was a gonorrhea.

If any doubt still remain with respect to the two diseases being of the same nature, it will be removed by considering that the matter produced in both is of the same kind, and has the same properties: the proofs of which are, that the matter of a gonorrhea will produce either a gonorrhea, a chancre, or the lues venerea; and the matter of a chancre will also produce either a gonorrhea, a chancre, or the lues venerea.

The following case is an instance of a gonorrhea producing a lues venerea. A gentleman twice contracted a gonorrhea, of which he was cured both times without mercury. About two months after each, he had symptoms of the lues venerea. Those in consequence of the first infection were ulcers in the throat, which were removed by the external application of mercury; the symptoms in consequence of the second were blotches on the skin, for which also he used the mercurial ointment, and was cured. With regard to the lues venerea proceeding from chancres, instances occur so frequently to every one's observation as to require no further proof here.

Since, then, it appears that the gonorrhea and chancre are the effects of the same poison, it may be worthy of inquiry, to what circumstances two such different forms of the disease are owing.

To account for these two very different effects of the same poison, it is only necessary to observe the difference in the mode of action of the parts affected when irritated, let the irritation be what it may. The gonorrhea always proceeds from a secreting surface, and the chancre is formed on a nonsecreting surface; and in this last the part to which the poison is applied must become a secreting surface

before matter can be produced. All secreting surfaces in the body being probably similar, one mode of application only is necessary to produce this disease in them all, which is by the poisonous matter simply coming in contact with them. But to produce the chancre, the venereal matter may be applied in three different ways: the first and most certain is by a wound, into which it may be introduced; the second is by applying the matter to a surface with a cuticle, and the thinner that is, it allows the matter to come more readily to the cutis; and the third is by applying the matter to a common sore already formed.

The poison, then, being the same in both cases, why do they not always happen together in the same person? For one would naturally suppose that the gonorrhea, when it has appeared, can not fail to become the cause of a chancre; and that this, when it happens first, must produce a gonorrhea. Although it does not often happen so, yet it sometimes does; at least there is great reason to believe so. I have seen cases where a gonorrhea came on; and in a few days after in some, in others in as many weeks, a chancre has appeared: and I have also seen cases where a chancre has come first; and in the course of its cure, a running and pain in making water have succeeded. It may be supposed that the two diseases arose from the original infection, and only appeared at different times; and their not occurring oftener together would almost induce us to believe it was so, since the matter is the same in both, and therefore capable of producing either the one or the other.

I suspect that the presence of one irritation in these parts becomes in general a preventive of the other. I have already observed, that the two parts sympathize in their diseases; and it is possible that that very sympathy may prevent the appearance of the real disease; for if an action has already taken place which is not venereal, it is impossible that another should take place till that ceases; and it is probable that this sympathy will not cease while the cause exciting it exists; and therefore when both happen in the same person at the same time, I suspect that either the urethra never had sympathized with the chancre, or if it did at first, that the sympathy had ceased, and then the venereal matter might stimulate the parts to action.



### Experiments Made to Ascertain the Progress and Effects of the Venereal Poison\*

TO ascertain several facts relative to the venereal disease, the following experiments were made. They were begun in May, 1767.

Two punctures were made on the penis with a lancet dipped in venereal matter from a gonorrhea; one puncture was on the glans, the other on the prepuce.

This was on a Friday; on the Sunday following there was a teasing itching in those parts, which lasted till the Tuesday following. In the meantime, these parts being often examined, there seemed to be a greater redness and moisture than usual, which was imputed to the parts being rubbed. Upon the Tuesday morning, the parts of the prepuce where the puncture had been made were redder, thickened, and had formed a speck: by the Tuesday following, the speck had increased and discharged some matter, and there seemed to be a little pouting of the lip of the urethra, also a sensation in it in making water, so that a discharge was expected from it. The speck was now touched with lunar caustic, and afterwards dressed with calomel ointment. On Saturday morning the slough came off, and it was again touched, and another slough came off on the Monday following. The preceding night, the glans had itched a good deal, and on Tuesday a white speck was observed where the puncture had been made: this speck, when examined, was found to be a pimple full of yellowish matter. This was now touched with the caustic, and dressed as the former. On Wednesday, the sore on the prepuce was yellow, and therefore was again touched with caustic. On Friday, both sloughs came off, and the sore on the prepuce looked red, and its basis not so hard; but on the Saturday, it did not look quite so well, and was touched again, and when that went off, it was allowed to heal, as also the other, which left a dent in the glans. This on the glans was filled up in some months, but for a considerable time it had a bluish cast.

Four months afterwards, the chancre on the prepuce broke out again, and very stimulating applications were tried; but these seemed not to agree with it, and nothing being applied, it healed

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\*A Treatise on the Venereal Disease, Part VI, Chap. 2, Section 2.

up. This it did several times afterwards, but always healed up without any application to it. That on the glans never did break out, and herein, also, it differed from the other.

While the sores remained on the prepuce and glans, a swelling took place in one of the glands of the right groin. I had for some time conceived an idea that the most effectual way to put back a bubo was to rub in mercury on that leg and thigh; and thus a current of mercury would pass through the inflamed gland. Here was a good opportunity of making the experiment. I had often succeeded in this way, but now wanted to put it more critically to the test. The sores upon the penis were healed before the reduction of the bubo was attempted. A few days after beginning the mercury in this method, the gland subsided considerably. It was then left off, for the intention was not to cure it completely at present. The gland, some time after, began to swell again, and as much mercury was rubbed in as appeared to be sufficient for the entire reduction of the gland; but it was meant to do no more than to cure the gland locally, without giving enough to prevent the constitution from being contaminated.

About two months after the last attack of the bubo, a little sharp pricking pain was felt in one of the tonsils in swallowing anything, and on inspection a small ulcer was found, which was allowed to go on till the nature of it was ascertained, and then recourse was had to mercury. The mercury was thrown in by the same leg and thigh as before, to secure the gland more effectually, although that was not now probably necessary.

As soon as the ulcer was skinned over, the mercury was left off, it not being intended to destroy the poison, but to observe what parts it would next affect. About three months after, copper-colored blotches broke out on the skin, and the former ulcer returned in the tonsil. Mercury was now applied the second time for those effects of the poison upon the constitution, but still only with a view to palliate.

It was left off a second time, and the attention was given to mark where it would break out next; but it returned again in the same parts. It not appearing that any further knowledge was to be procured by only palliating the disease a fourth time in the tonsil, and a third time in the skin, the mercury was now taken in

a sufficient quantity, and for a proper time, to complete the cure.

The time the experiments took up, from the first insertion to the complete cure, was about three years.

The above case is only uncommon in the mode of contracting the disease, and the particular views with which some parts of the treatment were directed; but as it was meant to prove many things which, though not uncommon, are yet not attended to, attention was paid to all the circumstances. It proves many things, and opens a field for further conjectures.

It proves, first, that matter from a gonorrhea will produce chaneres.

It makes it probable that the glans does not admit the venereal irritation so quickly as the prepuce. The chancre on the prepuce inflamed and suppurated in somewhat more than three days, and that on the glans in about ten days. This is probably the reason why the glans did not throw off its sloughs so soon.

It renders it highly probable that to apply mercury to the legs and thighs is the best method of resolving a bubo; and, therefore, also the best method of applying mercury to assist in the cure, even when the bubo suppurates.

It also shows that bubos may be resolved in this way, and yet the constitution not be safe; and therefore that more mercury should be thrown in, especially in cases of easy resolution, than what simply resolves the bubo.

It shows that parts may be contaminated, and may have the poison kept dormant in them while under a course of mercury for other symptoms, but break out afterwards.

It also shows, that the poison, having originally only contaminated certain parts, when not completely cured, can break out again only in these parts.

# Abstract of Current Syphilis Literature

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WM. H. DEADERICK, M.D., EDITOR

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SYPHILIS IN THE STATE OF MINNESOTA.—H. G. Irving, Minneapolis. The Journal Lancet, April, 1917.

Syphilis from an economic or a sociologic point of view is one of the greatest public-health problems of the day. Laws should be drawn placing syphilis in the group of infectious and contagious diseases. Regulation and control should rest with the board of health and a sufficient appropriation should be maintained to furnish adequate laboratory facilities and free treatment if necessary. Beds should be furnished in all medical institutions depending upon public funds for maintenance, where patients with infectious lesions might be detained until cleared up, and treatment should be not only furnished but obligatory. A campaign of education should be carried on by the State Board of Health and various medical societies.

THE DIFFICULTY OF DEMONSTRATING SPIROCHETES IN SYPHILITIC PLACENTÆ.—R. A. Bartholomew, Ann Arbor, Mich. The Journal of the Michigan State Medical Society, 1917, vol. xvi, p. 279.

Immediately after the expulsion of the placenta, a small piece about 2 cm. square through the entire thickness of the placenta was cut away and fixed at once in 10 per cent formalin. In three cases a small piece of cord taken from the umbilical end was also similarly fixed. After fixation for several days or more, small pieces averaging  $\frac{1}{2}$  cm. square, were cut from these specimens and placed in 96 per cent alcohol for twenty-four hours; (2) transferred to distilled water for one hour (3) transferred to 2 per cent silver nitrate solution in dark bottles and kept in incubator at 37° C. for three days; (4) washed in distilled water for two hours with one change; (5) put in solution of pyrogallie acid (16 gm.) water (400 c.c.) and 40 per cent formol (20 c.c.) for two days; (6) washed in distilled water one hour; (7) 96 per cent alcohol, twenty-two hours; (8) absolute alcohol, twenty-two hours, (9) xylol, one hour with one change; (10) paraffine sixteen hours; (11) embedded, blocked, and sectioned 3-5 microns thick, fixed to slide, paraffine removed, and mounted in bal-

sam. Examination was made under oil immersion lens, going over each section systematically with mechanical stage. With each set of tissues a piece of known syphilitic fetal liver was treated by the same technic as a control on the method. In view of the results obtained it would seem to be futile to attempt to diagnose syphilis by the demonstration of spirochetes in the placenta by the Levaditi method. The examination of the fetal liver in a suspected case, coming to autopsy, offers a much greater chance of success, and should be made use of as a practical method.

VISCERAL FINDINGS IN ONE HUNDRED SYPHILITICS.—Tasker Howard, Brooklyn, N. Y. *The American Journal of the Medical Sciences*, 1917, vol. cliv, p. 64.

Visceral syphilis is at least as common and much more serious than cutaneous syphilis, which has in times past been given the greater amount of attention. The manifestations of visceral syphilis are detectable in the early stages of the disease in a large proportion of cases. Such manifestations are about as readily controlled by proper treatment as are the visible signs of the disease. It is important, however, in view of the extreme seriousness of the later stages of visceral syphilis that the treatment be pushed energetically from the start in order to eradicate the disease while it is possible and before irremediable damage has been done. Furthermore, it is important that every patient with syphilis be carefully watched for signs of such visceral involvement as should indicate treatment besides the ordinary antisyphilitic measures. For example a dilating heart in early syphilis indicates rest just as clearly as though it were due to rheumatic carditis and the neglect of this precaution may leave the patient with a weak heart even though he be lucky enough to be cured of his syphilis. Cardiac dilatation of several weeks' duration sometimes occurs after the administration of salvarsan. To sum up, our medical wards will be deprived of their present generous supply of syphilitic wrecks, only when every syphilitic patient is treated early, thoroughly, persistently, and with painstaking consideration of his individual requirements.

ACUTE SYPHILITIC HEPATITIS.—H. L. McNeil, Galveston, Texas. *Interstate Medical Journal*, 1917, vol. xxiv; p. 685.

A lobular cirrhosis is perhaps best known. This is characterized by deep furrows, produced by cicatricial tissue which has taken the place of or has formed about previous gummata. Such a liver, the so-called "hepar lobatum," may be divided by the scars into a number of artificial lobes. This type of syphilis of the liver is quite characteristic. A diffuse syphilitic cirrhosis of the liver has been described, resembling grossly, that of the hypertrophic cirrhosis of Hanot except that jaundice is not commonly present in the syphilitic type. Such a liver

is generally uniformly enlarged. Perihepatitis caused by syphilis is generally admitted by pathologists to be quite characteristic of the disease. In the author's series of cases diagnosed clinically as syphilis of the liver, consisting of thirty-four cases, all of which have been observed during the past five years they have noted six cases in which the condition in question was strongly suspected for the following reasons. In all of these six cases the disease was strictly of an acute or subacute nature, none of the patients having been ill for more than six weeks before the consultation. In all cases definite hepatic enlargement was noted. Tenderness, not usually marked, however, was also noted over the liver in all six cases. Four of these patients had jaundice. Moreover, all six cases showed four plus Wassermann reactions, and finally all, except the one already reported, recovered promptly and completely under antiluetic treatment. The initial symptoms of acute syphilitic hepatitis are characterized rather by their paucity than by their seriousness. In the six cases in which this condition has been diagnosed, enlargement of the liver and tenderness over that organ have been the most constant findings, Jaundice, as has been mentioned, was present in four cases. Gastric symptoms, such as belching and a full dragging sensation in the epigastrium after eating, were the chief complaints of two patients. Pain was the chief complaint of one case. No fever was noted at any time in four out of six cases. In two cases, however, occasional irregular rises in temperature were noted. Enlargement of the liver was noted in all of these cases, varying in amount from two fingerbreadths to a hand's breadth below the costal margin. The surface of the liver was smooth in all cases and the edge was moderately soft in four. In two cases it was described as hard. The blood count was unchanged in all of these cases with the exception of a slight relative anemia in two. The white count was unchanged in all of these cases. It is interesting to note that all except one were negroes. In addition to the more chronic forms of syphilis of the liver it is probable that an acute or subacute syphilitic hepatitis occurs not infrequently. This condition is usually overlooked. It is the precursor, in all probability of the later cirrhotic changes met with in the livers of syphilitics.

SYPHILIS OF THE NOSE AND THROAT.—Joseph C. Beck, Chicago, Ill.  
New York State Journal of Medicine, 1917, vol. xvii, p. 290.

Primary chancre of the nose is usually considered rare. The clinical diagnosis of a primary sore is not always easy, especially if it is within the nose. Only after thoroughly cleansing the surface of the dirty yellowish green crusts, will one come on to the indurated area, which appears somewhat gray. This may or may not bleed, and is surrounded by a markedly swollen and congested mucous membrane. The regional lymphatic glands are usually enlarged. The Wassermann may not be positive but often is. The finding of the spirochete pallida from the scrapings of the surface will make the diagnosis

positive. It will not be long before the secondary roseola will make its appearance. The secondary stage manifests itself in the nose as an exanthema of the macular or papular type. Within the nose these reddish spots become frequently confluent and appear like any other form of eoryza. It is often spoken of as eoryza syphilitica. The only way one may differentiate it from a simple acute eoryza, aside from the spirochete and Wassermann, is that the secretion is not marked and the disease is more protracted. The tertiary stage is also known as the gummatous stage. Gumma of the nose most frequently develops from the periosteum, and this soon blocks the Haversian canals of the underlying bone, which brings about bone necrosis. This causes much purulent discharge which is characterized by its very foul odor. This process leads to true sequestration of bone and sloughing of the cartilages. The defect resulting either in the septum, lateral wall or floor of the nose is always much larger than the sequestrum or swelling, which is due to the fact that the endoarteritis is much further developed peripherally.

Pathological conditions that may be mistaken for a primary chanere of the pharynx are: a unilateral chronically enlarged tonsil with a superficial ulceration, a unilateral acutely swollen tonsil, simple ulcer of the tonsils, a single papule in a secondary lues, a single small ulcer of a gumma. The microscopie examination for spirochetes and the Wassermann in many cases will enable one to make a positive diagnosis, as will also a dose of salvarsan. The following pathologic conditions may be mistaken for the second stage pharyngeal syphilis: 1. Superficial cauterization especially with nitrate of silver. 2. Simple ulcerations of the pharynx, especially tonsils. 3. Aphthous pharyngitis. 4. Stomatitis catarrhalis in which the pharynx is also involved. 5. Herpes pharyngitis. 6. Pemphigus. 7. Tuberculous ulcerations. 8. Pharyngitis and stomatitis mercurialis. 9. Vincent's angina. 10. True diphtheria. The tertiary lesion begins in the form of an infiltrate or nodule which has a deep red color, and is sharply defined. Soon the center becomes soft and breaks down, forming an ulceration that has a sharp hard border, and is of a deep red color, the so-called punched out ulcer. It is usually covered with a thick dirty yellowish white membrane. When this lesion becomes secondarily infected with pus microbes, in addition to the further process of the gummatous change, there occurs the breaking down of the soft parts, destruction of bone, involvement of nerves and larger blood vessels. These changes lead to perforations, sequestra, hemorrhage and paralysis or intense neuralgias. These processes invariably extend to the nasopharynx and nose, as well as the larynx and trachea. Chanere in this locality has been observed a few times and invariably on the epiglottis. In the secondary stage the same lesions obtain as in the nose and pharynx, namely, patches or condylomata. At times the cords and ventricular bands become much infiltrated. While the epiglottis is most frequently the seat of these changes there have been observed mucous patches symmetrically located on the vocal cords. In the third

stage of syphilitic laryngitis we consider a number of changes; first, the nodular type; second, the solitary gumma; third, the diffuse gumma; fourth, the perichondritic form.

SYPHILIS AND PREGNANCY.—Burton Peter Thom, New York. *Medical Record*, 1917, vol. xci, p. 16.

Syphilis is always to be regarded as a grave complication of pregnancy. It increases puerperal morbidity more than any other cause. Many cases of nephritis occurring during pregnancy can be traced to syphilis. Sepsis is more apt to occur in syphilitic women than in those who are healthy. Cicatricial stenoses of the os due to syphilitic lesions may cause undue delay and complication of labor. The same is true to edema of the cervix due to active syphilis. Syphilis in the pregnant woman should be treated the same as when it occurs otherwise. That is, salvarsan, mercury and potassium iodide should be exhibited sufficiently and properly to cure the disease. In the treatment of pregnant women, however, there are certain refinements which should be observed in order to attain the best results for the mother and her unborn child. In giving salvarsan, it must be remembered that the drug has been known to cause premature expulsion of the fetus; but in the author's opinion this danger is remote. If the woman's veins are sufficiently prominent the salvarsan should be administered intravenously, unless she is suffering with myocarditis or if her blood pressure is abnormally high. If her veins are not prominent enough, and for the other causes mentioned, the salvarsan may be given by the rectum. A saline is given and after the bowels have moved, the lower bowel is thoroughly cleansed with a normal saline enema: after which the salvarsan solution is allowed to flow into the rectum through a catheter attached to a glass funnel. This method, while not much used, is almost as efficacious as when the drug is injected intravenously. It has the advantage of not increasing the blood pressure, does not produce water sickness, and is much easier to give to a nervous patient. Should the woman be threatened with eclampsia, salvarsan and mercury should be withheld until the urine is free from albumin.

SYPHILIS OF THE INTERNAL GENITAL ORGANS IN THE FEMALE.—Geo. Gellhorn and Hugo Ehrenfest, St. Louis. *The American Journal of Obstetrics and Diseases of Women and Children*, 1916, vol. lxxiii, p. 1.

It is at present impossible to estimate even approximately the full extent to which syphilis exists in the world. The latest statistics, which tend to show that 10 per cent of the male population of the United States are affected are probably far too conservative. Syphilis has always been assumed to be considerably commoner



among men than among women, but from certain investigations mentioned this supposition can not yet be accepted as conclusive. At any rate, syphilis is common enough in women to constitute a gynecologic problem in the widest sense. Not every disease in a syphilitic woman is syphilitic in nature; but syphilis, if present, will exert an influence of its own upon coexistent diseases. Moreover, latent syphilis prevails more in women than in men. The course of syphilis in men differs in many points from that in women. To instance but one of the differences mentioned, the relative frequency of tabes and paresis in the two sexes is well known.

Syphilis of the internal genitals in women presents a number of problems as yet unsolved. The question of infection by the sperm of a syphilitic man is discussed; as is, also the possibility of differences in the strains of spirochetes which might have a predilection for one or the other part of the female genital tract. There is, finally, the question whether certain parts of the genitals possess a sort of relative immunity. Secondary syphilitic lesions of the vagina are very rare. They occur either in the form of macules or of papules; the latter variety seems to be relatively more frequent. They have no symptomatology of their own and therefore are discovered only accidentally during an examination with the speculum. Tertiary leucic manifestations originate but very rarely in the vagina. When found there they represent, as a rule, the continuation of a like condition which had started from the vulva, the uterus, or adjoining organs. The isolated submucous gumma breaks down early and appears in the form of a more or less characteristic ulcer. The more destructive processes which eventually lead to the formation of fistulae and strictures, almost always originate in structures surrounding the vagina. Tertiary lesions of the vagina do not exhibit characteristic symptoms such as pain or discharge. The primary chancre of the cervix represents the best known and most common type of syphilitic affections of the female internal genitals. Its frequency has probably been overestimated. Statistics based on a large number of observations have never shown a frequency over 1.5 per cent of all primary chancres found on the genitals. It must, however, be admitted that in a considerable number of cases its presence on the vaginal portion of the cervix is overlooked. The primary chancre of the cervix does not give rise to any noteworthy clinical symptoms. Therefore, as a rule, a search for it is made only after the appearance of the secondary exanthema. Under normal conditions the primary lesion heals with such rapidity that its existence in a large percentage of the cases can only be surmised from certain findings which, in themselves, are not characteristic. A fairly large number of tertiary lesions of the cervix has been recorded in literature. To these, six personal observations have been added, one of which is not conclusive. The essential form is that of a gumma, which, in the majority of instances, undergoes necrosis and ulceration. Primary and secondary manifestations have not

yet been observed in the uterus. A few instances of gumma in the uterine wall have been recorded. It seems possible that the tubes may be the seat of luetic lesions, but the pathologic and clinical material on record is yet too incomplete to permit of positive assertions. Spirochetes have never been found in the tubes of syphilitic women. Various changes in the ovaries (simple enlargement, syphilitic oophoritis, tertiary sclerosis of ovary, ovarian gumma) have been described as typical expressions of the secondary and tertiary stages of luetic infection, but in no instance (with the possible exception of Hoffman's case) has positive proof been furnished that such alterations are actually due to a local luetic process. Syphilis of the pelvic cellular tissues appears in the form of a diffuse gummatus infiltration which secondarily involves the pelvic peritoneum. To the few cases on record a personal observation has been added. In almost all instances a wrong diagnosis of malignancy has been made. While actual and well-established facts regarding syphilis of the female genital organs are comparatively few in number in contradistinction to the many theories and the volume of literature on this subject, yet enough is known to compel and hold the interest of the gynecologist. Syphilis may cause organic lesions in all parts of the genital tract such as ulcerations and tumefactions. The gynecologist will be able to properly interpret and treat such lesions only if he is familiar with the local pathology of syphilis.

There are close analogies between the genital organs in the male and the female from a purely developmental and anatomic point of view. The fact that the ovaries correspond to the testicles, the tube to the epididymis, the uterus to the prostate has seemed, to many writers, sufficient to base deductions as to the pathology of syphilitic lesions in the female upon their knowledge of luetic lesions in the male. Such reasoning is faulty. Syphilis, in many respects, affects woman in a manner essentially different from man. After all, there is nothing in man to compare with disturbances of menstrual function which so often confront the gynecologist. Gynecology has, in the past, profited by the pioneer work of dermatology in the realm of syphilis. It is now time that the gynecologist should contribute his full share. There are still many mooted questions, such as syphilis without primary lesions (syphilis d'emblee) or the pathology of local lesions in the female genital tract, which the gynecologist is preeminently fitted to solve. He should also fall in line with the representatives of other specialties in advancing the problem of the relationship between cancer and previous syphilitic lesions in the same locality. Familiarity with syphilitic lesion in the genital tract must needs prove of eminent practical value to the gynecologist in view of the frequent confusion in the diagnosis of cancer and syphilitic ulcerations or gummata. That occasionally a patient is subjected to a serious radical operation who could have been cured by antileutic treatment there can be no doubt. A more

intimate interest in the problems of syphilis of the internal female genitals will advance gynecology both in its theory and in its practice.

UTERINE SYPHILIS.—John T. Williams, Boston. *Interstate Medical Journal*, 1917, vol. xxiv, p. 633.

Our knowledge of syphilis of the female genitals is markedly incomplete. While the infrequency with which primary lesions are found in the generative tract in women may be due in part to lack of systematic search for them, it also seems evident that syphilis does run a milder course in women and often escapes recognition. The later uterine manifestations of syphilis may take the form of ulcerations of the cervix, syphilitic endometritis, syphilitic lesions of the myometrium. Ulcerations of the cervix are most likely to be confused with malignant disease. The diagnosis must be made by the microscope. In specific lesions of the endometrium and myometrium the characteristic changes take place in the blood vessels and are similar to syphilitic arteritis elsewhere in the body. There is usually some increase in the fibrous tissue. The glandular elements are little if at all affected. The chief symptom ascribed to uterine syphilis is hemorrhage. While scientific accuracy demands the examination of all suspected tissue for specific lesions and if possible the demonstration of the spirochete pallida as well as a positive Wassermann reaction, the practitioner who is beyond the reach of laboratory facilities will be justified in administering anti-specific treatment in any case of uterine hemorrhage not relieved by curettage, and where there is no local or constitutional condition capable of causing such hemorrhage discovered after careful clinical examination.

SYPHILIS OF THE STOMACH.—Paul Rockey, Portland, Oregon. *North-west Medicine*, April, 1917.

In syphilitics with gastric complaints, where the cause is not in the stomach, it may be due to syphilis of organs in relation, as liver, pancreas, lymph nodes; to perigastric adhesions of syphilitic origin; to reflexes from syphilitic lesions at more distant points in the abdomen; to the toxemia and cachexia of the disease elsewhere than in the stomach; and to specific lesion in the brain; or to the gastric crises and gastric symptoms of tabes. Apparently syphilis of the stomach occurs in the tertiary stage or occasionally late secondary. Syphilis affecting the stomach directly might do so by its toxins affecting the stomach wall and the gross and the minute pathology of this change might be recognizable. Syphilis might affect the stomach by the presence of the spirochetes pallida in its layers. The therapeutic test, when used, should be adequate. Response to

it will probably be definite, but there are cases of syphilis usually resistant to antiluetic treatment. There are nonsyphilitic dyspepsias that may be benefited for a time by antispecific treatment. Simple gastric ulcer is subject to spontaneous cure, also to periodicity of course. Presumably syphilitic gastric ulcer is subject to similar phenomena. The prognosis of luetic gastric ulcer untreated, would presumably be worse than that of simple ulcer, but if treated, probably as good or better.

SYPHILIS OF THE STOMACH—REPORT OF A CASE.—Carrington Williams, Richmond, Va. *The Virginia Medical Semi-Monthly*, 1917, vol. xxii, p. 70.

This case has the typical symptoms and signs of syphilis of the stomach with the exception of the stomach analysis, which shows a higher acidity, subacidity or achylia being the rule. Briefly the symptoms are: Gradual onset twenty years after the initial lesion, pain almost constantly present and located in epigastric angle, vomiting without nausea, absence of blood in stool and vomitus, absence of physical signs except epigastric tenderness, normal blood count, Wassermann four plus.

A CONSIDERATION OF SYPHILIS OF THE STOMACH—ITS DIAGNOSIS AND TREATMENT.—B. B. Vincent Lyon, Philadelphia. *The Archives of Diagnosis*, April, 1917.

Pathologically the disease may show any one of the following forms: 1. A diffuse gastritis, involving the glandularis and submucosa. 2. Syphilitic ulcers, single or multiple frequently assuming serpiginous forms and having ragged overhanging edges and a smooth base. 3. A diffuse infiltration of the gastric wall which histologically must be distinguished from linitis plastica (unless these conditions are one and the same, as many clinicians believe) from a diffuse scirrhus carcinoma, and from a diffuse infiltration of a tuberculous type. 4. Pyloric stenosis. 5. Gumma, which may or may not give rise to a palpable tumor. Quite commonly we see the symptom-complex of an organic disease of the stomach involving both the motor and secretory mechanism. Aside from the comparatively few instances of motor obstruction due to syphilitic pyloric stenosis, the motor defect is much more commonly due to an extreme degree of atony associated with ectasia. The secretory defect is usually accomplished by the symptoms of a severe atrophic or sclerosing gastritis. Pyrosis is common and is of the type seen in the anacid states; sour eructations, together with the sense of an epigastric lump, weight or pressure, sometimes associated with bloating, the symptoms common to atony together with the fermentations seen in ectasia. In the ulcer form of the early symptoms may be a

profuse hematemesis, which is more apt to be recurrent than is common to simple gastric ulcer. There may be constitutional symptoms common to many diseases such as anorexia, loss of weight, weakness and emaciation. Excessive thirst is not uncommon. In ordinary cases the intestinal functions are properly performed; when deranged, constipation is apt to occur.

The gastric analyses much more commonly show a marked sub-acidity or anaecidity with a greatly diminished or absent enzyme activity, which is what one might expect to find associated with the pathologic defect of an atrophic gastritis. On the other hand, a few cases have been reported in which the hydrochloric acid content and peptic activity is normal, or even increased. An increase of endogenous mucus is generally the rule. Occult bleeding is frequently encountered both in the gastric filtrate and in the feces. The blood examinations when diagnostically helpful, usually show chloranemia, a moderate leukopenia, with a relative increase in the lymphocytes, and an absolute increase in the eosinophiles. The serologic examinations generally yield a definite positive Wassermann reaction, and is especially reliable when performed by the centrifuge method, and when checked by the Hecht-Weinberg Wassermann reaction as modified by Gradwohl. As in some other gastric conditions, the diagnosis may have been made by a process of exclusion. Particularly is this true in those individuals who give evidence of both a syphilitic infection and a gastric infection, but each independent of the other. In those cases in whom a positive history of a congenital or acquired syphilis can be obtained, the diagnosis can be made a clinically sound one if the serologic examinations are positive, and there is a cessation of gastric symptoms and a return to normal of the radiographic gastric contour after the exhibition of antiluetic therapy.

**SYPHILITIC ARTHRITIS—A QUESTION OF DIAGNOSIS.**—Archer O'Reilly, St. Louis. *Interstate Medical Journal*, 1917, vol. xxiv, p. 585.

In all joint cases a history of syphilis should be sought. If the patient does not admit lues, then suspicious signs should be looked for. Some patients deny syphilis intentionally, many others because they honestly do not know that they have had it. Unless an absolutely positive diagnosis of some other joint condition can be made, then syphilis should be suspected. In all cases absence of or slight pain, with functional disability, should be regarded with suspicion. The Wassermann is the most important aid to the diagnosis. It is believed that this test should be made in all cases of arthritis. Where this is impossible or inadvisable, it should be used in all cases where a positive diagnosis of some other joint condition can not be made. A positive Wassermann does not mean, however, that the joint lesion is necessarily syphilis. The diagnosis must be confirmed

by the therapeutic test. If the condition is syphilitic, there will be a marked and rapid improvement under antisyphilitic treatment; at times it seems almost like magic. There are also times when the Wassermann is negative, but where one feels that the condition is syphilitic. In these cases the therapeutic test is of great value. It is believed, however, that a positive diagnosis of joint syphilis should not be made unless the Wassermann is positive and is confirmed by the therapeutic test.

NOTE ON THE STAGES OF TABES DORSALIS.—Morris Grossman, New York. *Medical Record*, 1917, vol. xcii, p. 278.

The duration of the preataxic period may be influenced by age. The probable average preataxic period is three years. Women seem to have a shorter preataxic period than men. The average life expectancy of the bedridden tabetic is very much longer than that usually taught. The average age of the immobilized tabetic is 53 years. Most tabetics usually perpetuate the ataxic stage; in the small percentage of cases which become bedridden owing to uncomplicated ataxia, the average duration of the ataxia period is 4.11 years. Among those who become bedridden a short ataxic period usually follows a short preataxic period. This substantiates Maloney's contention that the deterioration of attitude is mainly mental and not structural deterioration. The short ataxic period in these bedridden cases is due to the same mental inferiority as is conducive to the short preataxic stage.

A COMPARATIVE STUDY OF DIFFERENT METHODS OF PERFORMING THE WASSERMANN FOR SYPHILIS.—J. Wheeler Smith, Jr., and Ward J. McNeal, New York. *The Journal of Immunology*, 1916, vol. ii, p. 75.

In a group of 110 syphilitic individuals in various stages of the disease, the cholesterin-reinforced antigen with incubation at 37° C. gave 58.2 per cent; the simple antigen at 37° C., 32.2 per cent; and the simple antigen at 8° C., 77.1 per cent of positive tests. In a group of 43 patients, probably syphilitic, the first method yielded 65.9 per cent; the second, 36.3 per cent; and the third method, 75.0 per cent of positive fixations. In a group of 59 patients, probably not syphilitic, the first method yielded 40.0 per cent; the second, 1.6 per cent; and the third, 5.0 per cent of positive tests. In a group of 265 nonsyphilitic patients, tests by all methods were negative throughout. The use of a simple alcoholic antigen, with the first incubation carried out in the ice box for four to twenty-four hours, is more sensitive in the detection of syphilis than the other procedures tested. Furthermore, a positive result thus obtained is

much more trustworthy evidence of syphilis than is a positive fixation with a cholesterinized antigen.

**TABES DORSALIS.**—Morris Grossman, New York. *New York Medical Journal*, 1917, vol. cvi, p. 402.

The average age of syphilitic infection, dated from the primary chancre, was 24.4 years. The average age of the onset of tabes in 238 cases was thirty-nine years. No detectable difference exists in the age of the onset of tabes in those patients treated with anti-syphilitic remedies and the age of onset in those untreated or presumably less treated. The average pre-tabetic interval is not greater than 14.6 years. The pre-tabetic interval in the young may, but seldom does, last for a shorter period than in the more mature. The resistance of the central nervous system seems to deteriorate with age.

**SYPHILIS OF THE CENTRAL NERVOUS SYSTEM.**—J. E. Auner, Des Moines, Iowa. *The Journal of the Iowa State Medical Society*, 1917, vol. vii, p. 174.

It is simple to recognize the expansive delirium of paresis or the ataxia of tabes, but the average practitioner should be on the alert for the early signs of these conditions. Pains in the lower extremities, if persistent, should be carefully differentiated from an ordinary sciatica; if associated with frequent headache, should speak to us of an early possible lues affecting the spine. Numbness of the toes is suggestive as an early sign as also failure of vision beyond what is normal for the patient's years. An irregular pupil should always send us to testing the knee jerk. Mental depression that can not be explained, particularly if accompanied by attacks of vertigo and failure of memory, should make us at once suspicious of a cerebrospinal luetic complication.

**SUMMARY OF THE WASSERMANN TESTS DONE DURING 1916 IN THE PHILADELPHIA GENERAL HOSPITAL.**—Randle C. Rosenberger, Philadelphia. *New York Medical Journal*, 1917, vol. cv, p. 1233.

The report on 5,106 Wassermann tests comprises the work done in this line during 1916 at the Philadelphia General Hospital. Most of these tests—4,430—were performed with the blood serum while the remainder—676—were with the spinal fluid. The ordinary routine technic was used, with three antigens, alcoholic extract of syphilitic liver, acetone insoluble lipoid, and cholesterinized alcoholic extract of beef heart. Controls were carried through in all cases. Taking the total number of all specimens of blood submitted there was a general average of 24.4 per cent positive, while the spinal

fluid gave a general average of 22.2 per cent positive. The latter figure is accentuated by the fact that a large number of specimens were from the insane department. In 133, positive reactions were obtained with the cholesterinized antigen alone, and in looking up the histories of these cases, it was found that a certain number gave more or less definite syphilitic histories. Unfortunately in a very large number of the total cases, no diagnosis was made at the time the serum was sent to the laboratory, and no diagnosis of a specific nature was found even after looking up the history sheet in the record room. In the author's opinion, the Wassermann test, using a reliable antigen, is the most valuable aid in the diagnosis of syphilis. Errors in the reading or recording of reactions may occur just as in any other scientific procedure. Where an antigen is made carefully and where titration is done regularly, where the control of each reagent used in the test is properly made there should be no great variation in the end result of this test.

THE SPINAL FLUID IN DIAGNOSIS, PROGNOSIS, AND TREATMENT OF CEREBROSPINAL LUES.—C. R. Ball, St. Paul, Minn. *The Journal-Lancet*, April, 1917.

In all nervous affections a spinal fluid Wassermann is of distinctly more value in diagnosis than a serum Wassermann. The spinal fluid reaction is frequently positive when the serum is negative. The frequency of the negative serum reaction in specific nervous affections has been the cause of many mistakes in diagnosis which would not have occurred if a spinal fluid Wassermann had been made. The reaction itself is less liable to error in the spinal fluid than in the blood. Cumulative evidence of its correctness may be obtained in the increase in the intensity of the reaction where larger amounts of fluid are used.

COMPARATIVE STUDY OF DIFFERENT ANTIGENS AND OF DIFFERENT TEMPERATURES OF INCUBATION IN THE WASSERMANN TEST.—J. Wheeler Smith, Jr., and W. J. McNeal, New York. *The Journal of Infectious Diseases*, 1917, vol. xxii, p. 233.

Wassermann tests have been performed on 501 identical specimens from 457 cases, by 6 different methods. The cases have been divided into 2 classes, on the bases of the histories, those giving histories of syphilis and those not giving such histories. The first class was called Group I. The second class was subdivided into several groups by a consideration of the symptoms and signs, including the Wassermann reaction. Group II A and II B are composed of cases which presented symptoms and signs of syphilis, more definite in II A than in II B. Both of these subgroups are considered as probably luetic. Group II C comprises cases in which the only evidence of syphilis



was complement fixation with one antigen. These cases are considered as probably not syphilitic. Group III is made up of the rest of the cases, in which there was no evidence of syphilis. The 6 methods consisted in the use of three different antigens; namely, alcoholic extract of beef heart, cholesterinized (Antigen B.H.C.) plain alcoholic extract of beef heart (Antigen B.H.P.) and acetone insoluble lipid antigen prepared from the same extract of beef heart (Antigen B.H.A.) under two sets of incubation conditions; namely, at 37° C., for 1 hour, and 8° C., for 4 hours. It was found that in cases of syphilis and in cases probably syphilitic, the highest percentage of positive reactions was obtained in Method 4, that is with cholesterinized antigen (B.H.C.) at 8° C., for 4 hours. The other methods, in order of value, were plain antigen (B.H.P.) at 8° C.; cholesterinized antigen (B.H.C.) at 37° C.; acetone insoluble antigen (B.H.A.) at 8° C.; B.H.A. at 37° C.; and B.H.P. at 37° C. Complement fixation was obtained in a small number of cases, which were probably not syphilitic. In all of these cases, the antigen which yielded the fixation was antigen B.H.C. sometimes at 37° C., sometimes at 8° C., and in a few instances both at 37° C., and at 8° C. A comparatively large number of negative controls were tested, in none of which, with the exception of the few cited above, which has been considered in a separate group, was any complement fixation obtained. The use of the cholesterinized antigen, with the first incubation, at 8° C., for 4 hours, constitutes a more sensitive test for syphilis than does any of the other methods examined. The cholesterinized antigen, both at 37° C. and at 8° C., is apt to yield nonspecific complement fixation. Therefore, in a diagnostic reaction, fixation with the cholesterinized antigen alone is, at best, of only doubtful significance. The simple extract antigen with the first incubation at 8° C., is more sensitive than the cholesterinized antigen at 37° C., and in this series it did not give any false positive reactions according to the available evidence. The acetone insoluble preparation, made according to the method of Noguchi, is less sensitive, either at 37° C., or at 8° C., than is the cholesterinized-reinforced antigen at either temperature, and is also less sensitive than the simple extract at 8° C. It is more sensitive than the simple extract at 37° C., and, in this series, has, according to the available evidence given no false reactions.

**A NEW MASTIC TEST FOR THE SPINAL FLUID.**—James A. Cutting, Agnew, Calif. *The Journal of the American Medical Association*, 1917, vol. xviii, p. 1810.

In brief, Emanuel's procedure was as follows: Five test tubes were used containing, respectively, 0.25, 0.125, 0.062 and 0.031 c.c. of spinal fluid mixed with 1 c.c. of a 1.25 per cent salt solution. The fifth tube contained no spinal fluid, and was used as a control.

Lastly 1 c.c. of an emulsion of mastic was added to each tube. In this manner the writer tested out the spinal fluids of thirty psychiatric patients. In paresis, tabes, and cerebrospinal syphilis there occurred a precipitation of the mastic in all the tubes, whereas in the normal fluid no flaking occurred except in the control. The mastic solution had to be made up fresh each time and quickly used. The mastic test, when taken together with the history and with the cell count, is of undoubted aid in the diagnosis of syphilis of the nervous system. By the addition of potassium carbonate, the degree of positiveness can be graded very accurately. By first incubating and then centrifugalizing, the test can be completed in two hours. It parallels quite closely the colloidal gold reaction, and is more easily interpreted and much more easily and quickly performed. In eighty-four cases of syphilis of the nervous system, the mastic test was uniformly positive.

THE WASSERMANN REACTION IN 1,266 CONSECUTIVE ADMISSIONS TO ELGIN STATE HOSPITAL.—Edgar W. Fell. *The Journal of Nervous and Mental Disease*, 1917, vol. xlv, p. 536.

Of 1,266 consecutive admissions to Elgin State Hospital 15.7 per cent gave distinctly positive serum Wassermann reactions. Of the 664 males 22.3 per cent were positive, of the 602 females 8.5 per cent were positive. Including positive spinal fluids in cases showing a negative serum the percentages are somewhat higher, male 23.3 per cent, female 8.8 per cent, total 16.4 per cent. Of the 148 males with positive serum, 120 belonged to the syphilitic psychoses. Of the 51 females, 26 belonged to this group. Excluding the syphilitic group of psychoses only 5.2 per cent of male, 4.4 per cent of female, and 4.8 per cent of total admissions gave positive serum Wassermann reactions. A high percentage of positives are found in none of the other large groups except chronic morphinism where in a total of 65 cases 24.6 per cent were positive. The explanation is offered that most of the morphine addicts are of a class likely to contract syphilis, more so than our general population. Of the 1,266 cases 161 belonged to the syphilitic group of psychoses, 131 male and 30 female. Of these 91.6 per cent of males, 86.6 per cent of females, and 90.68 per cent of the total had positive serum Wassermann. Fluid Wassermann tests were done on 372 of the cases. Excluding paresis it was done on 211 cases and in none of these was the test positive. Of paresis proper, 96 per cent had positive fluid, of the whole syphilitic group, 93.8 per cent. In the syphilitic group 3.7 per cent had both the serum and fluid positive. In the differentiation of cases in insane hospital work the following are found to be practical working rules. A positive serum Wassermann usually indicates paresis, especially in males, a negative serum does not exclude paresis, a positive fluid Wassermann practically always

indicates paresis, a negative fluid practically excludes paresis, a positive fluid Wassermann is by far the sign most constantly present in paresis and constantly absent in other psychoses which fact makes the laboratory findings more reliable criteria for diagnosis in doubtful organic cases, than uncertain clinical signs. The mistake is more likely to be made clinically of calling a case paresis when it is not than of calling paresis something else. An organic case with physical and mental findings uncertain, but suggesting paresis which on examination of the spinal fluid shows a negative Wassermann is very much more likely to prove not to have a syphilitic involvement of the cerebrospinal axis.

THE CLINICAL VALUE OF LUTIN TEST.—A. Stillians, Chicago. *Interstate Medical Journal*, 1917, vol. xxiv, p. 589.

The hope that the lutin test would be useful in determining a cure of syphilis was long ago given up, for it is not uncommonly negative in the latent cases. If the positive reactions in the latent cases are now shown to be due to the iodides, its usefulness will be still more limited. As long, however, as reliable positives are obtained in late cases of syphilis in which the Wassermann reaction is negative, the lutin reaction will continue to be of value in the diagnosis of syphilis. This occurred 27 times in the author's series of 255 syphilitics, that is, in nearly 20 per cent of the late cases, and had been reported by many other observers.

SALVARSAN AND INTRAMINE, WITH REFLECTIONS UPON CHEMOTHERAPY.—J. E. R. McDonagh, London. *The Lancet*, 1917, vol. xcxi, p. 914.

The arsenic in salvarsan does not attack the parasites directly, but only indirectly by increasing the oxidizing action of the protein particles in the serum and the plasma cells. If the patient is in the primary stage and treated with oxidizing agents only, should a recurrence appear it is most likely to simulate a chancre. If the patient has entered the generalization stage then the recurrence, if systemic, will be a gumma, and if nervous it will be one of cerebrospinal meningitis. Practical experience showed the author that the syphilitic symptoms disappear very much quicker under colloidal mercury than under salvarsan. The colloidal mercury, as is now prepared at the Crookes' Laboratories, is supplied as a 1 per cent emulsion, ready for injecting. The dose is from 5.0 to 15.0 c.c. and the drug can be injected intravenously to out-patients without causing more than a little abdominal pain, diarrhea, and tender gums, which usually disappear within 24 hours, or immediately after the intravenous injection of intramine. The tenderness of the gums begins to vanish while the patient is on the table. The writer

thinks it is clear that the inclusion of arsenic in our chemotherapeutic armamentarium is not necessary; that the combined use of oxidizing and reducing agents is better than the employment of only oxidizing or of only reducing agents; that the treatment of syphilis, so far as it affects the soldiers' stay in the hospital can be very considerably diminished in duration; and that the very severe after effects such as the increase in nervous syphilis, which will become more and more apparent, can be to a large extent, avoided. Nine intravenous injections may be given in a fortnight, in which period practically any syphilitic symptom may be made to disappear.

EXPERIMENTAL AND CLINICAL STUDIES OF THE TOXICITY OF DIOXYD-AMINO-ARSENOBENZOL-DICHLORHYDRATE.—J. Frank Sehamberg; John A. Kolmer, and Geo. W. Raiziss, Philadelphia. *The Journal of Cutaneous Diseases*, 1917, vol. xxxv, p. 286.

Salvarsan may be used in concentrated solutions up to 0.6 gm. in 10 c.c. in animals, without any evident increase of toxicity. The failure to neutralize solutions of salvarsan with alkali leads to an increase in toxicity of fifty to sixty per cent in solutions of  $\frac{1}{2}$  to 1 per cent concentration. The addition of a moderate excess of alkali beyond the amount required for neutralization does not increase the toxicity, as determinable by the duration of life of the experimental animal. It is possible, however, that it may have other untoward effects. The use of sterile fresh distilled water appears to possess advantages over sterile, stale distilled or nondistilled water as regards toxicity, although the difference in our experiments was not pronounced. Salvarsan in alkaline solution tends to undergo oxidation on standing, with consequent increased toxicity but this substance and its congeners vary considerably in the rapidity of oxidation and in the degree of associated toxicity. The drug should be used reasonably promptly after preparation. If two or three hours' delay is unavoidable, the solution should be kept in a cylinder, full to the stopper, so that no air is present. Several different types of reactive symptoms may occur after the use of salvarsan: (a) immediate, (b) early, and (c) delayed. The immediate symptoms are due to the paresis of the blood vessels; the early symptoms coming on a few hours after the injections are febrile and gastrointestinal, and the delayed symptoms may be referable to the brain or liver and gastrointestinal tract. There is no one cause of reaction. The etiologic factors in the production of reactive phenomena may be related to (a) the patient, (b) the technic, and (c) medicament. The authors believe that the most important factor in the causation of reactions is referable to the drug. They believe that the immediate vasoparetic reactive symptoms are due to traces of an unidentified impurity in the drug, which they have for convenience termed substance X, and are confident that these symptoms are not

due to "arsenoxide." Salvarsan and its congeners are not compounds of absolute chemical purity. The authors can not, therefore, expect absolute constancy in biologic effects. Salvarsan and its congeners may vary, within certain limits, in therapeutic effect, and to a greater degree in toxicity. The ampoules obtainable in the open market exhibit striking variations in toxicity. Even the poorest compounds, however, are tolerated by animals in much higher amounts than the maximum dose administered to man, so that there is nearly always a latitude of safety. The authors believe that the commercial products should be tested out intravenously as well as subcutaneously, and that they should be tolerated by rabbits in the dose of 60 mg. per kilo of body weight. Salvarsan is a safer substance than mercury and can be tolerated intravenously by white rats in fifty times the dose of the latter, weight for weight.

THE TREATMENT OF SYPHILIS.—H. K. Detweiler, Toronto, Canada. *The Canadian Medical Association Journal*, March, 1917.

The serologic improvement in the blood of cases of syphilis is often not indicated in the ordinary Wassermann test. By titrating the serums as described by the author, such cases, in practically every instance, can be shown to have definitely improved, often after only one injection. These findings constitute a strong justification for the persistence in treatment of so-called "refractory" cases.

DIARSENOL ADMINISTERED BY BRAYTON'S SIMPLIFIED METHOD OF GIVING SALVARSAN.—H. Townsend Low, Pueblo, Colo. *The Journal of the Colorado State Medical Society*, 1917, vol. xiv, p. 170.

This method is very simple, the time expended from the beginning of sterilization until the procedure is completed being only twenty minutes. The apparatus used consists of: (1) one 30 c.c. Luer syringe with needle, (2) one glass-stoppered 60 c.c. shaking bottle containing 25 glass beads, (3) one bottle of 15 per cent freshly prepared solution of sodium hydroxide, with medicine dropper, (4) one 50 c.c. glass funnel. The above described apparatus is sterilized by boiling in freshly distilled water in an eight-inch aluminum pan. The shaking bottle, containing 30 c.c. of water, is removed from the pan and the diarsenol added. It is then shaken until a clear amber solution exists. Fifteen per cent sodium hydroxide is then added until the precipitate which at first forms is dissolved. It is readily seen that both time and labor are saved by this method. The solution can be injected in from thirty to forty seconds, while with the gravity method it takes from ten to fifteen minutes. One can always be sure the needle has not passed through the vein by withdrawing the plunger slightly and noticing the blood mixing with solution, if

the needle is in the lumen of the vein. No air can enter the vein in using this method. In a series of twenty-five injections by this method, during the last two months the writer is convinced that the reaction is less than when using larger amounts of water. The so-called "water faults" are practically eliminated. Diarsenol gives less reaction than salvarsan. The clinical results are equally good. Its influence on the Wassermann test is as positive. Its toxicity is lower, and finally this method is an office, one man procedure.

THE ADMINISTRATION OF SALVARSAN IN CONCENTRATED SOLUTIONS.—  
Theo. H. Smith, Detroit, Mich. *Journal of the Michigan State Medical Society*, April, 1917.

The use of concentrated solution of salvarsan minimizes or does away with the ill effects due to imperfect distilled water, thus obviating one of the greatest dangers inherent in the hitherto accepted method. The fact that no apparatus is required except a syringe for salvarsan injections provides a great simplification of technic not only as regards bulk of apparatus but also as regards sterilization. There is reason to believe that concentrated solutions are more effective than dilute ones, in that the salvarsan in the former case is more slowly excreted. For the nervous patient, the intravenous injection of a syringeful of medicine is a procedure less taxing than the injection of a large quantity. This new method surpasses the old both in being a great saving in time and also in enabling the operator to dispense with the services of an assistant. One objection to the new method consists in the urgent necessity of a perfect technic in the intravenous injection itself. It is obvious that if the needle does not lie accurately within the vein, so that a small amount of the concentrated solution enters the perivascular tissue, the results may be even more disastrous than with the more dilute solutions. This danger must be faced of course, but need not deter the skillful operator. The degree of concentration permissible with salvarsan is a 1 to 3 per cent solution which is perfectly well borne. By the use of a small needle there is less danger of phlebitis or periphlebitis.

CRANIAL NERVE SYPHILIS; WITH TECHNIC OF TREATMENT.—Ford Eastman, Erie. *The Pennsylvania Medical Journal*, 1917, vol. xx, p. 478.

We must abandon the futile pill for the needle in the use of mercury. Results, both clinically and serologically, from intramuscular injections of the salicylate have been satisfactory to the writer; but only an occasional patient will bear the pain following these injections. For six months the writer has used the intravenous method of Loyd Thompson, preparing the bichloride with blood

serum or ascitic fluid in large quantities whenever the medium was available, preserving it in 5 c.c. ampoules. The preparation is time consuming, but the injections are effective and practically painless. With subdural methods, the only severe reactions have followed the use of the large amounts of serum required by the Swift-Ellis injection. Much less severe reactions follow the injections of more salvarsan and less serum by the technic of Ogilvie. Injections by the method of Gennrich, first given by Wile in this country using a solution of old salvarsan diluted with spinal fluid at the bedside, cause very mild reactions and appear to be equally effective.

THE TREATMENT OF LOCOMOTOR ATAXIA BY THE MALONEY METHOD.—Heinrich F. Wolf, New York. *New York Medical Journal*, 1917, vol. cvi, p. 121.

The method of Dr. Maloney has practically done away with all the shortcomings of the Frenkel method. There are two basic principles on which Maloney has founded his treatment, relaxation and reeducation. It is immediately noticeable, on looking at a tabetic, that all his attention is focused on his walking and that he keeps his entire body stiff. This is due to fear. The patient is conscious of the lack of natural control when he is walking and tries to compensate for it by keeping all the muscles, even those that are not needed for the particular action, in a tense state. The Frenkel method has tended to increase this tension. Maloney, however, set out to combat this and accomplish it by his method of relaxation. The difference between the Maloney treatment and the Frenkel treatment is very great and it lies particularly in the fact that the pure routine procedure, as it is practiced according to the Frenkel method, is impossible. Each joint and each part must be treated according to its condition. Resistance exercises must be graduated according to the strength of the muscles; the strength of the weak one must be educated up to the strength of the stronger one to produce the proper balance. Only after sensation has been improved can we proceed to crawling and walking exercises.

THE DIAGNOSIS AND TREATMENT OF PARESIS AND TABES WITH SPECIAL REFERENCE TO THE APPLICATION OF INTRADURAL REMEDIES.—John D. O'Brien, Canton, Ohio. *Ohio State Medical Journal*, May, 1917.

The efficacy of the treatment depends upon the early diagnosis of paresis, prompt treatment and the physical condition of the patient at the time of starting treatment. No type of method can be cited. Treatment must be individualized. While a general plan might be

adopted, each case must be studied according to its own peculiar conditions. Advanced cases, as a rule, show no reaction to the treatment clinically. They may, however, show a biologic change. The duration of the disease is not an indication of the severity of the condition. No set number of treatments can be utilized. The clinical and biologic changes are the best and most scientific guides. The biologic changes are the direct result of treatment. Tabetic cases respond more readily to treatment than cases of paresis. In some cases of paresis, treatment is very discouraging. The writer regards intraspinal medication as one of the most notable achievements of modern medicine. The intracranial route is a valuable adjunct to the intraspinal route; it is not an absolute necessity, as similar results are obtained by the intraspinal route. The best results are obtained by strenuous therapy. Instead of biweekly, injections should be given every five to eight days and cases should be followed up. The writer believes the Ogilvie modification superior to the Swift-Ellis plan, as we are better able to govern the dosage of salvarsan. Doses of salvarsan employed here varied from 1-8 mg. to 1-4 mg.

INTRASPINAL MEDICATION IN THE TREATMENT OF SYPHILITIC DISEASES OF THE NERVOUS SYSTEM.—Lewis M. Gaines, Atlanta, Ga. *Medical Record*, 1917, vol. xci, p. 1034.

The type of case which is benefited is first of all the early case of no matter what type. As a rule, those showing meningitic involvement as evidenced by high cell count and globulin content have a better prognosis. All agree that intraspinal therapy is practically free from danger, when due care is exercised in the preparation of the serum, in the technic of the administration, and in the after care of the patient. Fully 10,000 intraspinal injections have been given by those quoted in this paper, and only two or three unfavorable reactions have occurred. There are now in vogue three principal methods of intraspinal therapy, the Swift-Ellis method, the Ogilvie method, and the use of mercurialized serum. Each method has its advocates but the general trend of opinion seems to be in favor of the Ogilvie method. Good results are being obtained by all methods. The method of intraventricular therapy using serum prepared by Ogilvie's technic is reported only by Cotton and used by him in paresis. This method should merit much interest and promises unusually good results. The question of when to use intraspinal therapy is of importance. Many of those quoted in this paper use it in cases of neurologic syphilis when other methods fail. Others, including the writer, feel that valuable time may be saved in using the method from the beginning, especially in tabes, and paresis, while in cerebrospinal syphilis, intravenous salvarsan, mercury and potassium iodide may first be tried. Provided the method is used early and energetically and frequently, the four reactions may



be rendered permanently negative. In many cases, however, the Wassermann remains positive, though the cell count and globulin content are reduced to normal. Even in the presence of a positive Wassermann, there is frequently clinical improvement or apparent cure, while in the serologically negative cases there is corresponding clinical improvement. Those with the most extended experience now advocate intraspinal injections, every one to two weeks, or the intravenous injections once or twice a week, until the four reactions become negative. One should not conclude that a case is Wassermann-fast until after a prolonged trial of from 10 to 20 injections. Finally it must be emphasized that the early cases are the hopeful cases. Dead tissue can not be revived, but cases in which the disturbance is due to inflammatory reactions in the central nervous system, especially where meninges are bearing the brunt of the infection, are those in which brilliant results may be expected.

THE TREATMENT OF PARESIS.—Brittin D. Evans and Frederick H. Thorne, Morris Plains, N. J. *New York Medical Journal*, 1917, vol. cvi, p. 437.

Twenty-three patients were subjected to a series of intraspinal treatments with salvarsan, neosalvarsan, and albuminate of mercury. The smallest number of injections given to one patient was three, and the largest number twenty. The Wassermann reaction was temporarily reduced to negative with the blood serum of one patient and with the cerebrospinal fluid of three. Three patients showed some mental and physical improvement; ten died, four during the course of treatment and six several months after the treatments were discontinued; ten are living and are markedly demented. The authors have found that the intraspinal method of treating parietic dementia has had little or no therapeutic value in their series of cases.

TRUTH ABOUT INTRASPINAL INJECTIONS IN TREATMENT OF SYPHILIS OF NERVOUS SYSTEM.—Bernard Sachs, New York. *The Journal of the American Medical Association*, 1917, vol. lxi, p. 681.

In many particulars the advantages of the intraspinal method have been grossly exaggerated. The opinion has reached the laity, as promulgated by advocates of the intraspinal method, that general paresis can be cured and by the intraspinal method alone. The writer has personal knowledge of patients suffering from general paresis who have been treated persistently and on innumerable occasions by intraspinal injections administered by the chief apostles of this method. Some of these patients have had remission, but he doubts whether a single one has been definitely cured, while all the others have taken the natural but gradual course toward a fatal

termination. As for the remarkable reduction in the number of the lymphocytes and the change in Wassermann reaction claimed as a result of the intraspinal method, the writer can assert definitely, and the truth is already known to many, that the same changes have followed on intravenous injections, pure and simple, on repeated lumbar punctures, and on the introduction of the patient's nonsalvarsanized serum. Evidently the changes in the cerebrospinal content may be brought about in a number of different ways. In a large number of cases of tabes in which the patients had received numerous intraspinal injections without distinct improvement, a satisfactory result was obtained when intravenous treatment had been given in the intensive way. The best results are obtained in the cases of cerebrospinal syphilis that are either distinctly vascular in origin or are of the meningoencephalitic and meningomyelitic type.

The meningosyphilitic cases that so often suggest the possibility of latent paresis have been cleared up by a few salvarsan injections. There is often difficulty in establishing the differential diagnosis between these meningoencephalitic cases and those of true general paresis, so that the doubt may arise whether or not some of the cases of general paresis claimed as cures may not have been cases of this type. Meningomyelitis of the syphilitic type also yields to intensive treatment in the most satisfactory way. The spastic forms of spinal paralysis, the Erb type in particular which is in all probability a form of a true degenerative disorder, gives unsatisfactory results. As for tabes dorsalis, the writer can not claim any actual cure, but in reviewing his cases and seeing the patients months and years after the treatment had been instituted, there is no doubt that the patients were satisfied with the results of treatment; that they are better in many ways, and that we can not afford to disregard this treatment in tabes, without, however, claiming more for it than the results justify. There is no doubt that in many instances the vesical symptoms, the sexual impotence, the lightening pains, even the gastric crises have disappeared under intensive intravenous treatment. On the other hand, he is firmly convinced that in a large number of cases, particularly in private practice, in which the intravenous treatment has been given from the outset, the symptoms have progressed, and full-fledged tabes dorsalis has been developed in much the same way that it would have progressed if no active treatment had been given. The meningomyelitic forms of a tabetic type are the ones that can be benefited most readily. Finally, in general paresis salvarsan treatment has not helped the writer to effect a cure, but it has in some instances retarded the rapid progress of the disease. It has permitted, if not caused, marked remissions to be established for a considerable period of time. Some believe these remissions are the expression of antibody formation. Following the treatment, a number of the patients have been enabled

to return to their accustomed work for one, two or even more years, but he does not claim that a single patient suffering from general paresis has been cured of his disease by this or any other method. The problem for the future is to find some more diffusible remedy, lipoid soluble and less toxic than salvarsan that would be able to pass through the blood stream into the tissues of the brain through the choroid plexus into the spinal canal and attack the foci of spirochetes wherever they may happen to be located. We need not despair of the future, and the writer believes that if the neurologist and the laboratory worker will cooperate with one another in a rational and impartial manner an era of satisfactory antisyphilitic therapy may happily dawn on us.

THE TREATMENT OF SYPHILIS OF THE CENTRAL NERVOUS SYSTEM.—David A. Haller, Boston. *The Archives of Internal Medicine*, 1917, vol. xix, p. 997.

The irritating effect in the spinal canal of serum to which mercuric chloride has been added in the dose of 0.001 gm. is greater than that of 20 c.c. of salvarsanized serum separated from blood drawn thirty minutes after a dose of 0.6 gm. of salvarsan. The average effect on the laboratory findings in the spinal fluid from one dose of mercurialized serum is greater than from one dose of salvarsanized serum. Unpleasant symptoms are more common following intraspinal mercurialized serum than following salvarsanized serum. The greater irritation of the meninges from mercurialized serum prevents as rapid repetition of dosage as is possible with salvarsanized serum. Cases of general paresis, meningitis and cerebrospinal syphilis stand intraspinal treatment with mercurialized serum better than do cases of tabes dorsalis. It is particularly in cases of active syphilis of the meninges that the mercurialized serum is useful. Mercurialized serum has an advantage over salvarsanized serum in ease of preparation and in its keeping qualities. For these reasons it can be used under clinical conditions in which the use of salvarsanized serum is impossible, or at least very much more difficult.

TREATMENT OF PARESIS BY INJECTIONS OF SALVARSAN INTO THE LATERAL VENTRICLE.—Graeme M. Hammond; Norman Sharpe, and J. Wheeler Smith, New York. *Journal of the American Medical Association*, 1917, vol. lxix, p. 23.

The blood serums, the cerebral fluids and the spinal fluids of eleven patients with paresis undergoing intraventricular treatment with neosalvarsanized or salvarsanized serum were examined at irregular intervals, before treatment, after the first treatment, after the second treatment, and after the third treatment. Some patients have been examined since, after a lapse of from four to eight months. The

fluid changes were either nil or so slight as to be negligible in most instances. The alterations in the cell counts, subsequent to treatment, are not sufficiently striking or sufficiently uniform to warrant any general statement concerning the effect of these treatments on the cerebrospinal pleocytosis. The findings in the case of the globulin content are more susceptible to expression in a general statement. The globulin content, both in the cerebral and in the spinal fluids, was definitely diminished by this treatment. The colloidal gold reaction appears to be a valuable aid in the diagnosis of syphilis of the central nervous system, in particular of paresis. The performance of the test is easy requiring little apparatus, time or experience. Although a satisfactory theoretical basis for the reaction has not been advanced, the test seems to be of great practical value. The preparation of the colloidal gold solution presents some difficulties to the beginner, but in this as in everything else persistent effort with careful attention to details is certain to be rewarded with success. The essentials are chemically clean water and glassware and reagent chemicals.

RESEARCHES IN REGARD TO THE COAGULO REACTION OF THE SYPHILITIC SERUM.—Dr. Hisakiyo Uemura, Japan. *The American Journal of the Medical Sciences*, 1917, vol. cliv, 547.

In summarizing the results of his investigations the author asserts that the coagulo reaction is highly characteristic in the case of syphilitic serum, especially when the elaborated method described above is applied, and the sources of possible mistakes which we have also mentioned carefully avoided. In many cases this test is distinctly superior to the Wassermann reaction. After some practice one easily gains sufficient mastery over the technic on which it is based to be able to examine even a large number of sera without difficulty. It is hardly probable that the coagulo reaction will finally supercede the time-honored Wassermann reaction; but it does seem calculated both to furnish scientific research with valuable data in regard to the transformation of serum as wrought by syphilis, and also to facilitate the diagnosis of doubtful cases of syphilis, possibly also of certain apparently similar conditions.

VITILIGO AND SYPHILIS OF THE CENTRAL NERVOUS SYSTEM.—E. M. Auer, Indianapolis, Indiana. *The American Journal of the Medical Sciences*, 1917, vol. cliv, 596.

The author draws attention to the early occurrence, as compared with the other symptoms, of the skin manifestations, the appearance of which should make one strongly suspect a syphilitic condition in the individual, and, further, to the symmetric and

segmental distribution of the areas suggesting a lesion of the central rather than of the peripheral nervous system.

FURTHER STUDIES ON THE MODE OF ABSORPTION OF MERCURY IN THE INUNCTION TREATMENT OF SYPHILIS.—U. J. Wile and J. A. Elliott, Ann Arbor, Mich. *The Journal of Cutaneous Diseases*, 1917, vol. xxxv, 595.

In the present series of experiments the authors have attempted a comparison of the absorbability and elimination, particularly of calomel ointment and blue ointment. It was their thought that if calomel were as readily absorbed and as readily eliminated as the blue ointment, one might conclude that its therapeutic effect would be equally as rapid. In this event its greater cleanliness might justify replacing the blue ointment in our therapeutic armamentarium. They also attempted to determine not only the presence of mercury from parallel inunctions of mercury ointment and calomel ointment in the urine, but they investigated further the various body fluids, such as the stomach contents, the saliva, the blood, the milk, and the spinal fluid. An investigation of the sweat was obviously impossible, owing to the fact that they were employing the inunction method of treatment. In a series of experiments in which blue ointment and calomel had been rubbed in the skin, they were able to detect the mercury in the blood in the case of the blue ointment only after a considerable number of inunctions had been given. In the case of calomel they were unable to determine the presence of mercury in the blood as far as they tested, that is to say, it did not appear in the blood after the same number of inunctions with the blue ointment. From this experiment they conclude that mercury is eliminated into the blood stream more rapidly in the case of blue ointment than in the case of calomel. They attempted the detection of mercury in many different experiments following inunction of both calomel and blue ointment, and following injections of mercury salicylate, succinimide, and bichloride. In no case were they able to detect the faintest trace of mercury in the spinal fluid. Believing that perhaps the amount of fluid which was tested was too small, they collected fluid from several different cases that had been taking mercury in various forms for a long period of time. This experiment likewise proved negative. They were able, furthermore, to test the spinal fluid of a patient who died of mercurial poisoning from ingestion of sublimate. The spinal fluid in this case also failed to reveal the presence of mercury. The milk from various nursing women was tested following their inunction with both blue ointment and calomel. In both cases mercury in appreciable quantity was found as soon as tested for, that is, after one week of inunc-

tions, and undoubtedly would have been shown to be present earlier had they had the opportunity of testing for it. To avoid the possibility that the milk had been contaminated by the skin, the authors placed nursing women on the injection treatment and found mercury in the milk forty-eight hours after the injection with the bichloride. From this experiment it may justly be concluded that mercury is eliminated in very appreciable quantity by the lactiferous glands. The authors investigated the saliva of patients receiving the inunctions of both calomel and blue ointment and were able to detect mercury, although not in strikingly large quantities, in both instances. One case in which calomel ointment was used in connection with wet dressings of sublimate on an open syphilitic ulcer, yielded a very positive result in the saliva in the absence of any evident stomatitis or salivation. It may thus be concluded that the salivary glands excrete mercury even in the absence of excessive glandular activity. In washings from the stomach the authors were able to detect mercury following inunctions of both calomel and blue ointment. In both cases, however, the tests were made after several inunctions had been given. Complementary to experimental studies, further data should be forthcoming following a long series of clinical observations before the blue ointment should be discarded in favor of calomel ointment in the inunction treatment of syphilis. If such data will establish an equal therapeutic value for calomel, then it might well supersede blue ointment in our armamentarium as a cleaner method of anointing mercury.

THE TREATMENT OF TABES.—L. M. Gaines, Atlanta, Ga. *Southern Medical Journal*, 1917, vol. x, 777.

We feel justified in diagnosing the disease now before the appearance of Romberg's sign, ataxia, or even disturbances of the deep reflexes. We realize, further, that it is precisely at such an early period in the development of the disease that we can favorably affect it by treatment. If, associated with the foregoing, we have a positive reaction in the cerebrospinal fluid, indicating a chronic syphilitic meningitis, together with such pupillary phenomena as anisocoria, pupillary irregularity or sluggish reaction to light, the diagnosis of early tabes is most probable. Added to the foregoing symptoms, the loss of the Achilles tendon reflexes establishes the diagnosis of early tabes, even in the absence of those signs which we usually associate with tabes: Romberg's sign, marked sensibility loss, absent patellar reflexes, and Argyll-Robertson pupils. It is in such an early stage of the disease that the most successful treatment can be instituted. Since the experience of many years appears to demonstrate the hopelessness of the

disease, the introduction of a new therapy in the form of intraspinal medication, during the past few years, has been watched with the greatest interest. A method of treatment to stay the ruthless advance of so devastating a malady, which has hitherto resisted all treatment, is obviously of great importance. In the preparation of the serum given to the series of cases reported, the Swift-Ellis technic was followed except that the blood was withdrawn twenty to thirty minutes after the extravenous administration of salvarsan. Since prohibiting milk for some hours previous to treatment, the author has had much less severe reactions. Regarding the dangers of intraspinal treatment, when a careful observance of technic is followed, the procedure has proved safe. In all of the injections which the author has given, including those administered to the cases reported, no ill effects have been observed.

SYPHILIS OF THE NERVOUS SYSTEM IN SOME OF ITS CLINICAL AND PATHOLOGICAL MANIFESTATIONS.—W. G. Spiller, Philadelphia, Pa. *The American Journal of the Medical Sciences*, 1917, vol. cliv, 523.

In tabetic ocular palsies, as well as those recognized as syphilitic ocular palsies, the lesion is not primarily nuclear; but is in the nerve fibers as they leave the brain. The author is not prepared to state a conviction that primary nuclear palsy of the cranial nerves in tabes is impossible, but does believe that most tabetic cranial nerve palsies are primarily radicular, and that when nuclear changes are found in tabes they occur in cases of long standing. It is to be expected that when nerves have been degenerated near their nuclear origin during a period of years the nerve cells from which these degenerated fibers arise should show alteration. This viewpoint is of therapeutic, as well as pathologic, importance, for if the degeneration be in the nerve, we may expect recovery from persistent antisyphilitic treatment, provided the degeneration be not too intense and the treatment be begun early; whereas we may expect much less improvement if the cells of the origin be primarily affected. There are cases in which syphilitic ocular palsy is not caused by basal meningitis but softening implicating the nuclei or nerve fibers of the affected nerve. It is desirable to remember that permanent results were accomplished in the treatment of nervous syphilis in some cases before the days of salvarsan and the modern laboratory methods of investigation. Unfortunately, we must confess that our modern methods, while usually of great value, are not satisfactory in all cases of nervous syphilis, and that some cases do not respond to any treatment, and others may respond and then relapse. Syphilis affects not only the outer covering of the brain but also the lining of the ventricular spaces, and

may produce intense lesions here. Proliferations of the apendyma may be great, and the aqueduct may be occluded in the same way as frequently is one of the brain arteries, and in this manner hydrocephalus may result. Epilepsy is definitely caused at times by acquired syphilis, and it may be possible to trace the relation of cause and effect. In other instances of epilepsy the syphilis remains unrecognized. The Wassermann reaction may be negative, as it frequently is, when syphilis of the nervous system is of very chronic type.

PRESERVATION OF ANTISHEEP HEMOLYTIC AMBOCEPTOR IN GLYCEROL.—

R. O. Clock and S. D. Beard, New York City. *The Journal of Infectious Diseases*, 1917, vol. xxi, 408.

Fresh antisheep hemolytic amboceptors that were heated to 55° C. for one-half hour, and then mixed with an equal volume of glycerol did not deteriorate, but retained their original titer for three years. During that period, anticomplementary properties did not develop. The glycerol in the glycerolated antisheep hemolytic amboceptor did not influence the complement-fixation reaction. Fresh antisheep hemolytic amboceptors that were inactivated and then preserved in glycerol, as herein described, were not only remarkably stable, but were also protected from bacterial growth for a period of three years.

THE MASTICHE AND POTASSIUM PERMANGANATE TESTS APPLIED TO THE CEREBROSPINAL FLUID OF THE INSANE.—L. G. Lowrey, Boston. *The Boston Medical and Surgical Journal*, 1917, vol. cxxxvii, 115.

From the data presented dealing with the mastiche test on 36 fluids; and the permanganate test on 26 fluids from insane persons, the conclusion is drawn that neither of these tests is of sufficient value to become a part of the routine examination of spinal fluids from the insane.

THE WASSERMANN REACTION.—G. E. Henson, Jacksonville, Fla. *Southern Medical Journal*, 1917, vol. x, 786.

It is advisable for the serologist to abstain from going into the clinical features of a case. He should be guarded in submitting border-line reactions without commenting upon the significance of such reactions. Border-line reactions should not be accepted by the clinician as diagnostic of syphilitic infection unless supported by clinical symptoms. A single negative reaction should never be



allowed to exclude a diagnosis of luetic infection. The Wassermann test should be applied from time to time during the course of the disease to note the effect of therapeutic measures employed; and a case of syphilis should not be finally discharged until several negative reactions have been obtained, the last one to be at least eighteen months and preferably two years after treatment has been discontinued.

CONCLUSIONS DRAWN FROM A COMPARATIVE STUDY OF DIFFERENT METHODS OF PERFORMING THE WASSERMANN REACTION.—J. Broffenbrenner, Boston. *New York Medical Journal*, 1917, vol. cvi, 491.

The procedure the author recommends makes use of fresh unheated serum. The complement of the serum is titrated and utilized in the test, guinea pig complement being added when necessary. They reprecipitated acetone insoluble lipoids, of which one-tenth the anticomplementary dose still contains ten to one hundred antigenic units. The antihuman hemolytic system is used and the erythrocytes are sensitized before being added to detect the presence of free complement. Incubation for fixation of complement is best performed for thirty minutes at 37° C. in the water-bath. However, one can use ice box incubation for ten to fifteen hours as a presumptive test to eliminate the negative serums, and 37° C. incubation for five minutes to eliminate the strongly positive serums. For diagnosis, however, the one-half hour at 37° C. incubation is best.

CERTAIN TECHNICAL REFINEMENTS IN METHODS OF INTRAVENOUS INJECTION.—J. H. Stokes, Rochester, Minn. *Medical Record*, 1917, vol. xc, 535.

Depress the point of the needle without advancing. The bevel may be shut off against the top of the vein. Palpate the point with the free hand. It is easily recognized if it is still above the vein. In using a syringe, twist the piston in the barrel, pulling backward. It may be stuck. Slowly withdraw the point, if it can not be felt above the vein, lifting up as you do so. If it has entered the opposite wall it usually comes away with a palpable snap. Then quickly advance again, pressing down hard against the arm with the back of the syringe hand and lifting the point, to flatten the angle of the needle to the vein. If the above procedure fails twice, withdraw the needle until the point is just short of the skin puncture, and advance again after repalping the vein. This is a last resort. If the last procedure fails on one or two trials, withdraw the needle entirely and do not reintroduce it until satisfied as to its point, and that it is not plugged. Pressure on the vein for

five minutes with elevation of the arm while this is being done will often enable one to use the same vein again. Make no comments audible to the patient regarding the condition of your needle. Never try to inject through a hematoma. Use another vein or stop. Never inject and ask if it hurts, if you have the slightest reason to suspect that it will. To inject a little to find whether you are in the vein or not is absolutely inexcusable. Make every effort to have one puncture suffice, using the needle in various directions through the same puncture. In withdrawing Schreiber needles from the veins the aspiration of blood back into the tube by lowering the container, or washing the needle out with salt solution from a separate cylinder is unnecessary. Pressure made by the nurse over the needle as it is withdrawn, and the shutting off of the stream just back of the adapter and not higher up the tube, will prevent any leakage. After injection the needle can be rinsed by drawing distilled water through it, or the elastic recoil of the rubber tube will cause some of the solution to spurt through it when the compressing finger is released. It goes without saying that needles and solution should be fresh on clean patients or suspects, and that patients in florid stages should be treated last. The administration of intravenous medication to small children can be accomplished with ease as a rule through the external jugular vein, or through the anterior auricular or the more prominent scalp veins in heredo-syphilitic babies. We have thus far found this technic applicable to all cases and have had no occasion to attempt an injection into the superior longitudinal sinus through the anterior fontanelle. In all work with small children, fine steel hypodermic needles should be used.

THE HOSPITAL OPPORTUNITIES AND RESPONSIBILITIES TO THE SYPHILITIC.—Henry Rockwell Varney, Detroit. *The Journal of the American Medical Association*, 1917, vol. lxviii, 1953.

The syphilitics of a general hospital should all be in one department under the supervision of a group of specially trained men. This service should be wholly responsible for the absolute control and treatments of the syphilitics of that institution. When complications arise and the counsel of other specialists is necessary, cooperation is most essential. These specialists should examine and report to the head of the department recommendations for special treatment without any transfer to another department. The syphilitic cared for under such a system places confidence, first, in the syphilographer, and second, in the institution and its social service system of control. A small percentage of registered active syphilitics does not respond to periodic notification for return to the hospital for treatment. This irresponsible class should be compelled to return

by an order from the probate judge until it is considered uninfected. In no other disease is it more important that the confidence of the syphilitic in his physician be most firmly established. Rotation of service or the transferring to other services destroys this confidence, and its loss is most damaging and detrimental to the control of this class of hospital patients. This confidence must be maintained and continuously carried over for weeks, months, and years of observation. It is a fact that the syphilitic wanders from clinic to clinic, and shops from physician to physician principally because of a lack of interest of the staff physician. Now that we possess and have at our command the knowledge of the etiology, methods of early diagnosis, and specific treatment of this disease, we should strongly advocate the installing of a more uniform systematic method of medical service in our general hospitals for the control and treatment of the syphilitic.

CONSTRUCTIVE SUGGESTIONS TOWARD THE CONTROL OF SYPHILIS, GONORRHEA, PNEUMONIA, MALARIA, TYPHOID, AND TYPHUS FEVER.—  
Ira S. Wile, New York. *New York Medical Journal*, 1917, vol. cv, 1195.

While the ethical and moral sides of the venereal problem are the main issues to be met from the standpoint of public health, an earnest endeavor must be made to counteract the existing epidemic of syphilis and gonorrhea. Large as are the figures of reported cases in this city, they underestimate the total number of cases and are particularly lacking in accuracy for gonorrhea. A program for the prophylactic control of these diseases must be constructed on the basis of the recognition of syphilis and gonorrhea as diseases of more serious consequence to the community than practically any other disease with the possible exception of tuberculosis. From the health viewpoint the mode of attack must not involve the stigmatization of the sufferers as moral outcasts or degenerates. Prevention necessarily involves the cure of the victim, who otherwise is a constant menace to the community as a focus of infection. Our hospitals and dispensaries treating these diseases have failed to justify themselves by their results. The percentage of their established cures is disgracefully small, being in the large majority of institutions under fifteen per cent. This means a low grade efficiency which would scarcely be tolerated in any other field of human endeavor. To counteract these negative tendencies, dispensaries should be obliged to have a standardized equipment suitable to meet the needs of treatment. Hospital facilities should be available for incipient cases, without the necessity of segregation in special hospitals and without penalizing those infected because of the nature of the method of infection. From the standpoint of com-

numal usefulness hospitals can perform no greater service than by curing luetics and gonorrhoeics during the stage of greatest curability. It is reasonable to demand such service from all institutions receiving public moneys for caring for public charges. The community should be able to dictate the types of cases requiring hospitalization. If this can be done during poliomyelitis epidemic, it certainly is within its jurisdiction for syphilis endemic.

# INDEX TO VOLUME I

## AUTHORS INDEX

### B

BARKER, LEWELLYS F. The importance of a knowledge of syphilis, and especially of visceral syphilis for general medical diagnosis, 149

BARTLETT, C. J., and O'SILANSKY, A. L. A modified Wassermann technic based upon the rapid fixation of complement present in human serum, 776

BRAASCH, W. F. (*See* Judd and Braasch), 752

BRONFENBRENNER, J., and SCHLESINGER, M. J. A procedure for serum diagnosis of syphilis especially recommended for hospital routine, 406

### C

CARMAN, RUSSELL D. Syphilis of the stomach in its roentgenologic aspects, 111

CAULK, JOHN R., and GREDITZER, H. G. Observations on the bladder in diseases of the central nervous system—an analytical study of 117 cases, 42

COLLINS, JOSEPH. Unusual forms of syphilis of the nervous system with particular reference to their diagnosis, 63

CRAIG, CHARLES F. The practical application of the Wassermann test in the diagnosis and control of treatment of syphilis, 192

— The technic of the complement-fixation test for syphilis, 802  
CUMMINGS, ROLAND. (*See* Fulton and Cummings), 663

### D

DEBUYS, L. R. Lues and the baby, 117  
DOWNEY, JESSE WRIGHT, JR. The value of the complete examination of the ear in syphilis, 616

### F

FOX, HOWARD. Palmer syphilides, 422  
FULTON, DUDLEY, and CUMMINGS, ROLAND. Luetin reaction in cardio-vascular-renal diseases, 663

### G

GRADWOHL, R. B. H. Some remarks on the serological diagnosis of syphilis with special reference to the Hecht-Gradwohl test, 450

GREDITZER, H. G. (*See* Caulk and Greditzer), 42

### H

HARRIS, THOMAS J. Gumma of the nose—a clinical note, 60

HAZEN, H. H. Syphilis as a cause of chronic urticaria, 750

— The teaching of syphilis, 135

HUNTER, JOHN. Epoch-making contributions to the study of syphilis, 821

## J

JOHNSON, CHARLES D. Serological examination of over two hundred children from the open air schools of St. Louis, 606

JUDD, E. S., and BRAASCH, W. F. The advisability of prostatectomy in the presence of cord lesion, 752

## K

KNAPP, E. V. Wassermann reaction in four hundred cases investigated by group study methods, 772

KOLMER, JOHN A. (*See* Schamberg, Kolmer, and Raiziss), 1

## L

LAFFERTY, R. H., and THOMPSON, S. R. The presenting symptoms in three hundred consecutive cases of syphilis, 624

LAMB, ROBERT SCOTT. Subconjunctival infections of salvarsanized serum in the management of ocular syphilis, 58

## M

MCNEIL, H. L. Syphilis of the stomach, 91

— Syphilis of the liver, 738

MONTGOMERY, DOUGLASS W. Rabelais' conception of syphilis, 221

— The behavior of the lymphatic system in syphilis, 729

MORTIMER, J. L. Syphilis of the duodenum, 473

## N

NOGUCHI, HIDEYO. Spirochaetes, 261

## O

OGILVIE, HANSON A. The treatment of general paresis—a report of fifty-five cases, 509

O'LEARY, PAUL A. (*See* Stokes and O'Leary), 629

O'SHANSKY, A. L. (*See* Bartlett and O'Shansky), 776

## P

PETERSON, REUBEN. A plea for routine Wassermann examinations for obstetric and gynecologic patients in hospital and general practice, 211

POTTENGER, FRANCIS M. A comparison of some of the important phenomena in syphilis and tuberculosis, 718

PROESCHER, FREDERICK; SEIL, HARVEY A.; and STILLIANS, ARTHUR W. A contribution to the action of vanadium with particular reference to syphilis, 347

PUSEY, WILLIAM ALLEN. The sanitary attack upon syphilis, 125.

## Q

QUALLS, GUY L. Some observations on latent or clinically inactive syphilis in the Canal Zone, 712

## R

RAIZISS, GEORGE W. (*See* Schamberg, Kolmer, and Raiziss), 1

RAVOGLI, A. A few points on public prophylaxis against syphilis, 788

REASONER, MATHEW A. Experimental syphilis produced through local applications to mucous membranes, 478

RHOADS, T. L. The influence of the Wassermann test on surgery, 468

## S

SCHAMBERG, JAY FRANK; KOLMER, JOHN A.; RAIZISS, GEORGE W. The chemotherapy of mercurial compound, 1

- SCHLESINGER, M. J. (*See* Bronfenbrenner and Schlesinger), 406
- SEIL, A. (*See* Proescher, Seil, and Stillians), 347
- SMITHIES, FRANK. Syphilis of the stomach, 100
- STILLIANS, ARTHUR W. A proposed standardization of the Wassermann reaction, 767
- (*See* Proescher, Seil, and Stillians), 347
- STOKES, JOHN H., and O'LEARY, PAUL A. The provocative Wassermann test in the clinical diagnosis of syphilis, 629
- SWIFT, HOMER F. Observations on types of response in treatment of syphilis of the central nervous system, 524

## T

- THOMPSON, LOYD. A note on the treatment of syphilis with galyl, 665
- Complement fixation in syphilis, 555

- Syphilis of the thyroid, 179
- THOMPSON, S. R. (*See* Lafferty and Thompson), 624

## W

- WATKINS, W. WARNER. The roentgen diagnosis of lung syphilis, 760
- WARTHIN, ALDRED SCOTT. Syphilis of the pulmonary artery; syphilitic aneurysm of left upper division: Demonstration of spirochete pallida in wall of artery and aneurysmal sac, 693
- WHITE, CHARLES J. The place of syphilis in our medical schools and hospitals, 144
- WILE, UDO J. The spirochetal content of the spinal fluid of tabes, general paresis, and cerebrospinal syphilis, 84
- WOOLLEY, PAUL G. A series of ruptured aortic aneurysms, 426
- Aortic aneurysms and dilatations, 582
- Cases of hypertrophic cirrhosis of the liver, 649





## GENERAL INDEX

### A

- Aachen methods in the treatment of gastric crises, 691
- Absorption of mercury in the inunction treatment of syphilis, 687
- A comparison of some of the important phenomena in syphilis and tuberculosis, 718
- Acute syphilitic hepatitis, 829
- Addison's disease of syphilitic origin, 232
- Administration of arsenobenzol by mouth, 501
  - of salvarsan in concentrated solutions, 846
- Advisability of a more general use of the Wassermann test in the service, 681
  - of prostatectomy in the presence of cord lesion, 752
- Agar, luctin reaction produced by, 687
- American association for the control of syphilis, 692
- Aneurysms, aortic, and dilatations, 582
  - of pulmonary artery, 693
  - ruptured, 426
- Annular macular syphilide, 669
- Aortic aneurysms and dilatations, 582
- Arsenical preparations, treatment of syphilis with, 502
- Arsenobenzol, administration by mouth, 501
- Arterial hypertension due to, or associated with, syphilis, results of treatment, 253
  - hypertension with special reference to syphilis, 746
- Arthritis, syphilitic, 837
- Atypical primary lesions in the early diagnosis of syphilis, 239

### B

- Baby, lues and the, 117
- Bilateral Charcot hips occurring simultaneously, 490
- Bladder, observations on the, in diseases of the central nervous system, 42
  - syphilis of, 234, 488
- Bone and joint lesions, syphilitic, simulating tuberculosis, 487
- Bones and joints in early syphilis, 230
  - syphilis of long, 490

### C

- Campaign against venereal disease, medical profession and, 251
- Canal zone, latent syphilis in the, 712
- Carbohydrates, influence on spirochetes, 483
- Cardiac crises in tabes dorsalis, 236
  - syphilis, 487, 672
- Cardio-vascular-renal disease, luctin reaction in, 663
  - syphilis as a factor in, 486
- Cases of hypertrophic cirrhosis of the liver, 649
- Causes of arterial hypertension with special reference to syphilis—a clinical inquiry, 746
- Central nervous system, oculocardiac reflex in syphilis of, 676
- Cerebral syphilis, 257
- Cerebrospinal cases, treatment of, 505
  - fluid in fifty cases of cerebrospinal syphilis, study of, 495
  - syphilis, cerebrospinal fluid in, 495
  - response in treatment of, 524
  - spinal fluid in, 840
  - treatment of, 507

- Certain phases of syphilis in the negro female from the standpoint of medical diagnosis, 240
- technical refinements in methods of intravenous injection, 857
- Chaneres, extragenital, 484
- Charcot hips, bilateral, 490
- Chemotherapy of mercurial compounds, 1
- Cirrhosis, hypertrophic, of the liver, 649
- Clinical course and physical signs in hereditary syphilis of early age, 248
- signs and diagnosis of late hereditary syphilis, 235
- value of the luetin test, 843
- Clinico-anatomical investigation of a rapidly fatal case of general paralysis due to acquired syphilis, 677
- Coagulo reaction of the syphilitic serum, 852
- Colloidal gold solution, standard method for making, 494
- test, 680
- Combination of sulphur and mercury in the treatment of syphilis, 499
- Committee on uniformity of the Wassermann reaction, report of, 495
- Comparative study of different antigens and of different temperatures of incubation in the Wassermann test, 840
- study of different methods of performing the Wassermann test for syphilis, 838
- study of salvarsan and neosalvarsan in the treatment of syphilis, 500
- study of the luetin and Wassermann reactions in infancy and childhood, 245
- Complement fixation in syphilis, 555
- test for syphilis, technic of, 802
- using human complement, 682
- simplified, 493
- Conclusions drawn from a comparative study of different methods of performing the Wassermann reaction, 857
- Congenital lues, 677
- Conjugal paresis, 235
- tabes dorsalis, 676
- Consideration of syphilis of the stomach, its diagnosis and treatment, 836
- of the serobiologic reaction after five years of observation, 492
- Constructive suggestions toward the control of syphilis, gonorrhea, pneumonia, malaria, typhoid, and typhus fever, 858
- Contribution to the action of vanadium with particular reference to syphilis, 347
- Control of syphilis, American association for, 692
- Cranial nerve syphilis; with technic of treatment, 846
- Criminals, syphilis among confined criminals, 482
- Critical study of one hundred twenty cases of late syphilis, 485

## D

- Death after salvarsan, 501
- following intravenous injection of salvarsan, two cases, 253
- Delayed negative Wassermann reaction, 245
- Dental stigmata, heredosyphilitic, 250
- Diabetes and syphilis, 231
- mellitus and syphilis, 489, 672
- Diagnosis and general treatment of syphilis, 238
- and treatment of paresis and tabes with special reference to the application of intradural remedies, 847
- and treatment of syphilis, 254, 491
- of syphilis, 239
- Hecht-Weinberg-Gradwohl test in, 492

- Diagnosis of syphilis,—Cont'd  
 modern, 688  
 of the nervous system, 687  
 of tabes dorsalis, 496  
 Diagnostic and prognostic significance  
 of spinal fluid findings in syphilis, 680  
 Diarsenol administered by Brayton's  
 simplified method of giving salvarsan, 845  
 Difficulty of demonstrating spirochetes  
 in syphilitic placenta, 828  
 Dioxydiamino-arsenobenzol-dichlorhydrate, toxicity of, 844  
 Drug-fastness of spirochetes to arsenic, mercurial and iodide compounds in vitro, 483  
 Duodenum, syphilis of, 473  
 Dyschromias of syphilis, 485

## E

- Early diagnosis of tabes dorsalis, 496  
 Ear, value of the complete examination of, in syphilis, 616  
 Effect of potassium iodide on luetin reaction, 246  
 Epididymitis, syphilitic, 232  
 Epoch-making contributions to the study of syphilis, 821  
 Erythrocytes, preservation of, for Wassermann reaction, 494  
 Experimental clinical studies of the toxicity of dioxydiamino-arsenobenzol-dichlorhydrate, 844  
 syphilis produced through local applications to mucous membranes, 478  
 Extragenital chancres, 484

## F

- Fetal and placental syphilis, 249  
 Fever, syphilitic, 239  
 in relation to gynecologic and obstetric practices, 671

- Few points on public prophylaxis against syphilis, 788  
 Four plus Wassermann, 686  
 Frequency of hereditary syphilis, 227  
 Further studies on the mode of absorption of mercury in the inunction treatment of syphilis, 853

## G

- Galyi in the treatment of syphilis, 665  
 Gastric crises treated by Aachen methods, 691  
 General paralysis, rapidly fatal case of, 677  
 paresis, treatment of, 509  
 Genital organs in the female, syphilis of, 832  
 Genitourinary organs, syphilis of, 489  
 Group study methods, Wassermann reaction in four hundred cases investigated by, 772  
 Gynecologic and obstetric practice, syphilitic fever in, 239  
 Gynecology, Wassermann reaction in, 243

## H

- Headache, puncture, 686  
 Heart, syphilis of, 487, 672  
 Hecht-Gradwohl test, 450  
 Weinberg-Gradwohl test in the diagnosis of syphilis, 492  
 Hepatitis, acute syphilitic, 829  
 Hereditary syphilis as a cause of chronic invalidism, 491  
 clinical course and physical signs, 248  
 clinical signs and diagnosis of, 235  
 frequency of, 227  
 in the light of recent clinical studies, 236  
 treatment, 259  
 Heredosyphilitic dental stigmata, 250  
 Herpes zoster in tabes dorsalis, and general paralysis of the insane, 678

Hospital opportunities and responsibilities to the syphilitic, 858  
 How shall latent syphilis be treated, 254  
 Human complement in complement-fixation test, 682  
 Hypertension, arterial, with special reference to syphilis, 746

## I

Icterus gravis syphiliticus; its relation to acute yellow atrophy, 674  
 Immunity and luetin skin reaction, 242 in syphilis, 228  
 Immunologic studies on pure cultures of various spirochetes, 667  
 Importance of a knowledge of syphilis, and especially of visceral syphilis for general medical diagnosis, 149  
 Infancy and childhood, luetin and Wassermann reactions in, 245  
 Influence of carbohydrates on the cultivation of spirochetes, 483  
   of potassium iodide on the luetin test, 247  
   of Wassermann test on surgery, 468  
 Intensive treatment of syphilis, 253  
 Intestines, syphilis of, 670  
 Intraspinal medication in the treatment of syphilitic diseases of the nervous system, 848  
   treatment of neurosyphilis with the standardized serum, 506  
   syphilis of the central nervous system, 258, 847, 848, 849, 850  
 Intraspinal injections of neosalvarsanized serum in nervous and mental diseases, 690  
   treatment of neural syphilis with mercury, a new method, 504  
 Intravenous injection, technical refinements in methods of, 857  
 Inunction treatment of syphilis, 687  
   treatment of syphilis, mode of absorption of mercury in, 853

## J

Joints and bones in early syphilis, 230

## L

Lange's colloidal gold test, 680  
 Latent or clinically inactive syphilis in the Canal Zone, 712  
   syphilis and diabetes, 231  
   study of one hundred twenty cases, 485  
   treatment, 254  
   visceral lesions in, 675  
 Lectures on the early diagnosis and treatment of syphilis, 491  
 Liver, syphilis of, 738, 829  
 Locomotor ataxia (*See* Tabes dorsalis)  
 Lues and the baby, 117  
   maligna, with report of two cases, 234  
 Luetin reaction, effect of potassium iodide on, 246, 247  
   in cardio-vascular-renal disease, 663  
   in infancy and childhood, 245  
   in syphilis produced by agar, 684  
   skin reaction and immunity, 242  
   test in nonsyphilitic patients, provocation of, 682  
 Lung, two cases of syphilis of, 234  
 Lymphatic system, behavior of, in syphilis, 729

## M

Margin of error in Wassermann reaction, 241  
 Mastiche and potassium permanganate tests applied to the cerebrospinal fluid of the insane, 856  
 Mastic test for the spinal fluid, 841  
 Medical profession and the campaign against venereal disease, 251  
   schools and hospitals, place of syphilis in, 144  
 Mercurial compounds, chemotherapy of 1  
 Mercurialized serum and bichloride of mercury, 498

Mercurialized serum,—Cont'd  
     in the treatment of syphilis of  
     the central nervous system, 507  
     serums, 497, 498  
 Mercurial medication with spinal drain-  
     age, 505  
     preparation, a new, in the treatment  
     of syphilis, 499  
 Mercuric chloride test for the diagno-  
     sis of syphilitic infection, 679  
 Mercury, absorption of, in the inune-  
     tion treatment of syphilis, 687, 853  
 Minnesota, syphilis in, 828  
 Modified Wassermann technic based  
     upon the rapid fixation of com-  
     plement present in human serum,  
     776

## N

Negro female, certain phases of syph-  
     ilis in, 240  
 Neosalvarsan, symptoms following in-  
     jection of, 499  
     toxic effects, 689  
 Nervous and mental diseases, intra-  
     spinous injections of neosalvar-  
     sanized serum in, 690  
     system, diagnosis of syphilis of, 687  
     syphilis of, 247, 255, 256, 257, 258,  
     691, 838, 839, 840, 846, 847, 848,  
     849, 850, 851, 852, 854, 855  
     unusual form of syphilis of, 63  
 Neural syphilis, a new method for in-  
     traspinous treatment of, 504  
 Neurologic symptoms, syphilis with, 248  
 Neurosyphilis, intraspinal treatment of,  
     with standardized serum, 506  
 New mastic test for the spinal fluid,  
     841  
     mercurial preparation in the treat-  
     ment of syphilis, 499  
     method for intraspinous treatment of  
     neural syphilis with mercury, 504  
 Nose and throat, syphilis of, 830  
 Note on a case with severe gastric cri-  
     ses treated by Aachen methods,  
     691

Note,—Cont'd  
     on the stages of tabes dorsalis, 838  
     on the treatment of syphilis with  
     galyol, 665  
 Notes on the teaching and treatment of  
     syphilis, 504

## O

Observation on the bladder in diseases  
     of the central nervous system, 42  
     transmission of syphilis with particu-  
     lar reference to a paternal source  
     of infection, 227  
     types of response in treatment of  
     syphilis of the central nervous  
     system, 524  
 Obstetric and gynecologic clinic, syph-  
     ilis in, 233  
 Ocular crises, tabetic, 491  
     syphilis, subconjunctival injections  
     of salvarsanized serum in, 58  
 Oculocardiac reflex in syphilis of the  
     central nervous system, 676  
 On the reliability of the Wassermann  
     reaction, 681

## P

Palmar syphilides, 422  
 Paresis and tabes, treatment of, 847  
     conjugal, 235  
     treatment of, 509, 849, 851  
 Paretic, shall we treat the, 504  
 Paternal source of infection, 227  
 Persistence of active lesions and  
     spirochetes in the tissues of clin-  
     ically inactive or "cured" syph-  
     ilis, 229  
 Placentæ, syphilitic, difficulty of dem-  
     onstrating spirochetes in, 828  
 Placental and fetal syphilis, 249  
 Place of syphilis in our medical schools  
     and hospitals, 144  
 Plea for routine Wassermann examina-  
     tion for obstetric and gynecol-  
     ogic patients in hospitals and  
     general practice, 211  
 Postmortem Wassermann reactions, 685

Potassium iodide, effect of, on luetin reaction, 246, 247  
 permanganate and mastiche tests applied to the cerebrospinal fluid of the insane, 856  
 Practical application of the Wassermann test in the diagnosis and control of treatment of syphilis, 192  
 Pregnancy and syphilis, 832  
   Wassermann test in, 246  
 Presenting symptoms in three hundred consecutive cases of syphilis, 624  
 Preservation of antishoop hemolytic amboceptor in glycerol, 856  
   of erythrocytes for the Wassermann reaction, 494  
 Principles of the treatment of syphilis, 252  
 Procedure for serum diagnosis of syphilis especially recommended for the hospital routine, 406  
 Prophylaxis against syphilis, a few points on, 788  
 Proposed standardization of the Wassermann reaction, 767  
 Prostatectomy in the presence of cord lesion, 752  
 Provocation of the luetin test in non-syphilitic patients, 682  
 Provocative Wassermann test in the clinical diagnosis of syphilis, 629  
 Psychoses, syphilitic, 237  
 Public health, syphilis in its relation to, 250  
 Pulmonary artery, syphilis of, 693  
 Puncture headache, 686

## Q

Quantitative effect of salvarsan on the Wassermann reaction, 244

## R

Rabelais' conception of syphilis, 221  
 Recent advances in the treatment of syphilis, 690

Relation between diabetes mellitus and clinical syphilis, 672  
   of the luetin skin reaction to immunity in syphilis, 242  
 Reliability of the Wassermann reaction, 681  
 Report of a case of tabetic ocular crisis, 491  
   series of sixty-one extragenital chancres, 484  
   of the committee on uniformity of the Wassermann reaction, 495  
 Researches in regard to the coagulo reaction of the syphilitic serum, 852  
 Response in the treatment of syphilis of the central nervous system, 524  
 Results of treatment in arterial hypertension due to or associated with syphilis, 253  
 Roentgen diagnosis of lung syphilis, 760

## S

Salvarsan, administration of, in concentrated solutions, 846  
   and intramine, with reflections upon chemotherapy, 843  
   and neosalvarsan in syphilis, 507  
   death following intravenous injection of, 253  
   effect of, on Wassermann reaction, 244  
   fatalities, 253, 501  
   in the treatment of double infection, tuberculosis and syphilis, 252  
 Salvarsanized serum, subconjunctival injections of, in ocular syphilis, 58  
 Salvarsan, toxicity of, 500  
 Sanitary attack upon syphilis, 125  
 Selective action of spirochetes, 679  
 Series of ruptured aortic aneurysms, 426  
 Serobiologic reaction, consideration of, after five years of observation, 492

- Serologic examination of over two hundred children from the open-air schools of St. Louis, 606
- Serum diagnosis of syphilis, 406, 450
- Serums, mercurialized, 497, 498
- Shall we treat the paretic, 504
- Simplified complement-fixation test, 493
- Sketch of my research on syphilis, 678
- Sodium cocodylate in the treatment of syphilis, 503
- Some general information concerning the diagnosis and treatment of syphilis, 254
- observations on latent or clinically inactive syphilis in the Canal Zone, 712
- phases of experimental syphilis with special reference to the question of strains, 482
- remarks on the serologic diagnosis of syphilis with special reference to the Hecht-Gradwohl test, 450
- Specificity of the Wassermann reaction, 245
- Spinal drainage, mercurial medication with, 505
- fluid, a new mastic test for, 841
- findings in syphilis, diagnostic and prognostic significance of, 680
- in diagnosis, prognosis, and treatment of cerebrospinal lues, 840
- spirochetal content of, 84
- Spirochetal content of the spinal fluid of tabes, general paresis, and cerebrospinal syphilis, 84
- Spirochete, demonstration of, in wall of artery and aneurysmal sac, 693
- Spirochetes, 261
- difficulty of demonstrating, in syphilitic placenta, 828
- drug-fastness of, 483
- immunologic studies on pure cultures of, 667
- influenced by carbohydrates, 483
- Spirocheta pallida* or *treponema pallidum*, 227
- Spirochetes, selective action of, 679
- Standard method of making uniform colloidal gold solution, 494
- Stigmata, dental, 250
- Stomach, syphilis of, 91, 100, 235, 485, 489, 673, 835, 836
- Studies of the stomach in syphilis, 489
- Study of cerebrospinal fluid in fifty cases of cerebrospinal syphilis, 495
- involvement of the bones and joints in early syphilis, 230
- proximo and acro-ataxia in tabes dorsalis, 237
- sodium cocodylate in the treatment of syphilis, 503
- two hundred ninety postmortem Wassermann reactions, 685
- Subconjunctival injections of salvarsanized serum in the management of ocular syphilis, 58
- Sulphur and mercury in the treatment of syphilis, 499
- Summary of the Wassermann tests done during 1916 in Philadelphia General Hospital, 839
- Surface tension and Wassermann reaction, 492
- Surgery, influence of Wassermann on, 468
- Symptoms following injection of neo-salvarsan, 499
- presenting, in three hundred consecutive cases of syphilis, 624
- Syphilis a disease of diminishing severity, 667
- and pregnancy, 832
- and trauma, 230
- as a cause of chronic urticaria, 750
- as a factor in the production of cardio-vascular-renal disease, 486
- in its relation to public health, 250
- in the state of Minnesota, 828
- in the University of Michigan obstetric and gynecologic clinic, 233
- of long bones, 490
- of the bladder, 234, 488
- of the body of the uterus, 233

## Syphilis,—Cont'd

- of the central nervous system, 839
- of the duodenum, 473
- of the genitourinary organs, 489
- of the internal genital organs in the female, 832
- of the liver, 738
- of the nervous system, 247, 255, 257, 691
- of the nervous system in some of its clinical and pathological manifestations, 855
- of the nose and throat, 830
- of the pulmonary artery: syphilitic aneurysm of left upper division: demonstration of spirochete pal-lida in wall of artery and aneurysm sac, 693
- of the stomach, 91, 100, 235, 485, 489, 673, 835, 836
- of the stomach; a case of hour-glass contraction, 235
- of the stomach; report of a case, 836
- of the thyroid, 179
- problem among confined criminals, 482
- with neurologic symptoms stimulating other conditions, 248
- without chancre in women, 228
- Syphilitic arthritis, a question of diagnosis, 837
- bone and joint lesions simulating tuberculosis, 487
- disease of the thymus in infants and the mode of origin of the Dubois abscesses, 488
- epididymitis, 232
- fever in relation to gynecologic and obstetric practice, 239, 671
- psychoses associated with manic depressive symptoms and course, 237

## T

- Tabes and paresis, treatment of, 847
- dorsalis, 839
- a study of proximo and acro-ataxia in, 237

## Tabes,—Cont'd

- cardiac crises in, 236
- conjugal, 676
- early diagnosis of, 496
- stages of, 838
- treatment of, 854
  - by the Maloney method, 847
- Teaching and treatment of syphilis, 504
- of syphilis, 135
- Test for syphilis, 244
- Testicle, syphilis of, treatment with salvarsan and neosalvarsan, 251
- Testicular syphilis, 232
- Throat and nose, syphilis of, 830
- Thymus, syphilis of, 488
- Thyroid, syphilis of, 179
- Toxic effects from neosalvarsan, 689
- Toxicity of salvarsan, 500
  - of the present supply of salvarsan and neosalvarsan, 500
- Transmission of syphilis, 227
- Trauma and syphilis, 230
- Treatment and diagnosis of syphilis, 254, 491
  - of cerebrospinal syphilis with report of cases, 505
  - of general paresis, 509
  - of hereditary syphilis, 259
  - of latent syphilis, 254
  - of locomotor ataxia by the Maloney method, 847
  - of paresis, 849
    - by injections of salvarsan into the lateral ventricle, 851
  - of syphilis, 238, 845
    - intensive, 253
    - of the central nervous system, 255, 256, 257, 258, 851
    - of the central nervous system with intraspinal injections of mercurialized serum, 507
    - of the testicle with salvarsan and neosalvarsan, 251
    - principles of, 252
    - recent advances in, 690
    - with arsenical preparations, 502
  - of tabes, 854
- Truth about intraspinal injections in



- treatment of syphilis of the nervous system, 849
- Tuberculosis and syphilis, comparison of some of the important phenomena, 718
- and syphilis, salvarsan in treatment of, 252
- and Wassermann reaction, 241
- syphilitic bone and joint lesions simulating, 487
- Wassermann in, 246
- Two cases of late congenital lues, 677
- of probable syphilis of the intestines, 670
- of syphilis of the lung, 234

## U

- Unusual forms of syphilis of the nervous system with particular reference to their diagnosis, 63
- Urticaria, syphilis as a cause of, 750
- Uterine syphilis, 835
- Uterus, syphilis of, 233

## V

- Value of the complete examination of the ear in syphilis, 616
- of the Wassermann test in pregnancy, 246
- Vanadium, action of, in syphilis, 347
- Venereal disease, medical profession and the campaign against, 251
- Visceral findings in one hundred syphilities, 829
- lesions in latent syphilis, 675
- syphilis, importance of a knowledge of, 149
- Vitiligo and syphilis of the central nervous system, 852

## W

- Wassermann examinations for obstetric and gynecologic patients, 211
- paradoxus, 496
- reaction, 492, 493, 494, 495, 496, 554, 629, 679, 681, 682, 685, 686, 767, 772, 776, 802, 838, 839, 840, 856, 857
- as carried out by the department of health, 679
- delayed negative, 245
- effect of salvarsan on, 244
- in four hundred cases investigated by group study methods, 772
- in gynecology, 243
- in infancy and childhood, 245
- in its relation to tuberculosis, 241
- in one thousand two hundred sixty-six consecutive admissions to Elgin State Hospital, 842
- in two hundred fifty-one tuberculous dispensary cases, 246
- margin of error in, 241
- proposed standardization of, 767
- specificity of, 245
- surface tension and, 492
- technic based upon the rapid fixation of complement present in human serum, 776
- test, a comparative study of different methods of performing, 838
- comparative of different antigens and temperatures of incubation, 840
- influence on surgery, 468
- in pregnancy, 246
- practical application of, 192
- Women, syphilis in, without chancre, 228

## SUGGESTIONS TO CONTRIBUTORS

"The four rules for the preparation of an article will then be: (1) Have something to say; (2) Say it; (3) Stop as soon as you have said it; (4) Give the paper a proper title."<sup>1</sup>

Let your phraseology express one meaning and one only. Be clear.<sup>2</sup>

**Manuscript.**—Manuscripts should be typewritten, with wide margins, and double spaced, on one side of paper 8½ by 11 inches in size. The original copy should be sent to the "Journal" and the carbon copy retained by the author. Number the leaves consecutively, beginning with the title page. Put your name and address on the manuscript.

**Illustrations.**—Illustrations should be clear, preferably pen-and-ink drawings. Of photographs send a good print rather than a negative. Have lettering parallel to the bottom and top margins, and of sufficient size to be clear if cut is to be reduced. Tracings should be in black-and-white; avoid colors. Write your name on back of each picture; number them in one series (Fig. 1, etc.) to the end, and indicate in margin of the manuscript about where each is to be printed. See that the text references and "figures" correspond. Legends for illustrations should be written on a separate sheet.<sup>3</sup>

**Bibliographic References.**—Give only references actually consulted. If an article is known only through an abstract give reference to the abstract in addition to that of the source. References are printed to be of help in further reading; therefore they must be complete, concise, and correct. Follow the style of the "Index Medicus" and "Index-Catalog of the Library of the Surgeon-General's Office." Be conservative in the use of abbreviations.<sup>4</sup>

**Arrangement.**—As authors are quoted in the text give each a number in the order of citation, and number the bibliographic reference with the same number. Arrange the references in a list at the end of the article in the order of the numbers (see below), or arrange items in alphabetical order according to last names of authors, and distinguish between articles by the same author by the use of the date after his name in the text.

**Foot-notes.**—Where an author wishes to use foot-notes at bottom of each page instead of the bibliography at end of article, the foot-notes should be written in the text, but separated from it by horizontal lines above and below, or *better*, place them at bottom of each page. Use figures to indicate these foot-notes, and number consecutively (1, 2, 3, etc.) throughout the article. If in addition to the bibliography mentioned above it is desired to use foot-notes on certain pages, these can be indicated by an asterisk (\*).

**Final Reading.**—Let some one other than the author read the manuscript with these directions in mind.

**Shipment.**—Send manuscript flat, postage paid, to the editor, Dr. Loyd Thompson, Dugan-Stuart Building, Hot Springs, Arkansas.

**Proof-reading.**—Read carefully, with special attention to spelling of names and bibliographic data. Make corrections *in the margin* only with lines drawn from the revision to the point of change in the text. Answer queries in the proof by making correction or crossing out the query. Verify your references from the sources, not from your carbon copy.

### References. (Read these.)

<sup>1</sup>Billings, J. S.: Our Medical Literature, Trans. VII Intern. Med. Congress, Lond., 1881, i, 54-70.

<sup>2</sup>Mayer, Emil: Medical Literature and its Preparation, Med. Record, N. Y., 1915, lxxxvii, 1019-1021.

Allbutt, T. C.: Notes on the Composition of Scientific Papers. London, Macmillan, 1904.

McCrae, Thomas: The Use of Words, Jour. A. M. A., Chic., 1915, lxxv, 135-139.

<sup>3</sup>Suggestions to Medical Authors, issued by the A. M. A. Press, Chic., A. M. A., 1914 (?).

<sup>4</sup>Place, F.: Bibliographic Style in Medical Literature. Med. Record, N. Y., 1913, lxxxiii, 157-160.









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